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The Effect of Shipping Stresses on Vaccine Re-dispersion Time

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ABSTRACT

A case study is presented for a vaccine drug product (DP) that showed variable re-dispersion times between syringes within a given DP lot and between different DP lots when shipped from the manufacturing site to the receiving site. A simulated shipping study was designed to understand the effect of individual shipping stresses on re-dispersion time and product quality. Shipping stresses simulating shock/drop, aircraft, and truck vibrations were applied separately to 3 syringe orientations, namely tip up, tip down, and tip horizontal (TH). Results from the simulated shipping study showed that shock/drop reduced re-dispersion time while truck and aircraft vibrations increased re-dispersion time in the tip down orientation. The dissimilar effects of different shipping stresses on re-dispersion resulted in the observed intra and inter DP lot variability in re-dispersion time. Shipping stresses did not impact re-dispersion in the TH or tip up orientation. No vaccine product quality attributes or physical properties were affected by shipping stresses. Actual shipping results correlated well with simulated shipping data. Because re-dispersion time was influenced mainly by shipping stress and syringe orientation, the mitigation measure to reduce end-user re-dispersion time was to implement the TH orientation for DP syringes during shipment and storage.

Introduction

Insoluble aluminum-containing salts (aluminum phosphate or aluminum hydroxide) are widely used as adjuvants in vaccines. The addition of insoluble adjuvants to a vaccine drug product (DP) results in a suspension. A number of commercial aluminum-based vaccines (e.g., Prevnar 13®, Cervarix®, Havrix®, Gardasil®, etc.) instruct in their package inserts to shake vigorously immediately prior to use. On April 26, 2010, WHO recommended the recall and destruction of all lots of SHAN 5 vaccine as a precautionary measure following reports of white sediment sticking to SHAN 5 vaccine vials that was difficult or impossible to re-suspend.[1] Therefore re-dispersion of vaccine suspension is an important consideration during vaccine development. We present a case study for a vaccine suspension where variable and increased re-dispersion times were observed during the course of development not only between different DP lots but also between syringes within a given DP lot.

Abbreviations used: DP, drug product; TD, tip down; TH, tip horizontal; TU, tip up.

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Materials and Methods

Materials

Vaccine DP syringes (1.0 mL short from Beckett-Dickinson) filled with 0.5 mL suspension containing multiple adsorbed antigens on aluminum salt (aluminum phosphate) at pH 6 in buffered saline matrix were produced by Pfizer, Inc.

Methods

Re-dispersion Time

Syringes were allowed to equilibrate at room temperature for at least 60 min prior to re-dispersion time measurement. The syringe was held between the thumb and index finger, with the tip cap facing the thumb and shaken vigorously. The time it took to obtain a uniform white suspension free of any large particles was recorded using a timer. Re-dispersion time was measured on 3 separate syringes and the reported time is thus an average of 3 measurements. In order to minimize the variation that could result from different analysts performing the test, the re-dispersion time measurement was conducted by the same analyst for all samples. In general, the standard deviations associated with these measurements are small (±3 s) for easy to re-disperse syringes but are significantly large

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(±40 s) for hard to re-disperse syringes (because of the variability between the hard to re-disperse syringes). The authors would like to point out that the re-dispersion results presented here should be viewed as a trend rather than an absolute value. Note devices were not used to measure re-dispersion time because device variability was found to be much greater than human variability and because of the need to mimic the act of re-dispersion in a clinical setting.

Simulated Shipping

The simulated shipping study was carried out at Pira International, Inc. (Huntington Beach, CA) on a vibration table employing the International Safe Transit Association 3A profile. The syringes were arranged in 3 different orientations: tip cap down (TD), tip cap up (TU), and tip cap horizontal (TH). Re-dispersion time was tested for each lot and orientation before and after the stress studies. For the shock/drop test, 9 free fall drops from a height of 18 inches were utilized, with a 36-inch drop height for drop 8. For the aircraft and truck vibration, syringes were vibrated for 24 h each using the aircraft-Jet random vibration profile and steel Spring Truck random vibration profile, respectively.

Actual Shipping

Syringes were shipped from the manufacturing site to the testing site in 3 controlled orientations (TU, TD, and TH) along shipping routes that included road, water, and air.

Settling Rate

DP syringes were vortexed to ensure dispersion. Excipient buffer was added to the suspension and the mixed diluted sample (~1 mL) was dispensed into a 1.5-mL semi-micro cuvette and measured at 645 nm every 15 s for 1 h with Shimadzu UV-1800 Spectrophotometer (Shimadzu Scientific Instruments, Japan). At least 3 syringes were measured per lot.

Particle Size Distribution

DP syringes were vortexed to ensure dispersion. Suspension was injected into a 1.7 mL micro tube. The micro tube was inverted 10 times before the reading was collected on a Malvern Mastersizer 2000 with small volume sample dispersion system (Malvern Instruments Ltd., UK). At least 3 syringes were measured per lot.

In Vitro *Antigenicity*

In vitro antigenicity was measured using conformation-specific monoclonal antibodies and a Bioveris M384 analyzer. Antibody recognizing functional and non-overlapping sites on the antigen was used to capture and detect the antigen. The *in vitro* antigenicity is reported as a percentage, relative to the standard.

Concentration and Bound Antigen

The suspension samples were centrifuged at 10,000 rpm for 10 min. The supernatant was assayed for protein concentration by ion-exchange chromatography. The amount of protein adsorbed was determined by subtracting the amount of protein in the supernatant from the total amount.

Purity

Samples were analyzed using a reversed-phase high-performance liquid chromatography Agilent 1100 series system (Agilent Technologies, Santa Clara, USA) fitted with an analytical C18 column (Waters Corporation, Milford, MA). A gradient elution was performed at a flow rate of 1 mL/min with solvent A (0.1% trifluoroacetic acid in water) and solvent B (acetonitrile). All the chromatograms were monitored at UV 214 nm.

Results

Factors Influencing Re-dispersion Time for the Studied Vaccine

During the development of the vaccine DP, we noticed that it was difficult to re-disperse some of the DP syringes to obtain a homogeneous white suspension. The time to completely re-disperse the suspension in the syringes (referred to as re-dispersion time) was found to vary significantly between syringes within a given DP lot and between different DP lots. The re-dispersion time was less than 10 s for easy to re-disperse syringes and greater than 30 s for hard to re-disperse syringes.

Our initial findings demonstrated that shipping, syringe orientation, and age of vaccine suspension were key factors that influenced the re-dispersion time. Syringes shipped or stored in the TD orientation exhibited the longest re-dispersion times (on an average 161 s and as high as 250 s) followed by TU (on an average 53 s) and TH orientations (on an average 35 s). Syringe orientation had a greater impact than age on re-dispersion time, with age having the greatest impact on the TD orientation.

A preliminary simulated shipping study on the vaccine DP syringes was conducted where a combination of stresses (shock/drop followed by aircraft vibration followed by truck vibration followed by another shock/drop) was used as is the industry standard for simulated shipping studies. This study produced confounding data on re-dispersion time, where simulated shipping either helped decrease re-dispersion time for some syringes or increased re-dispersion time for other syringes (data not shown).

Effect of Individual Simulated Shipping Stress Elements on Re-dispersion Time

In order to further understand the interplay between shipping and syringe orientation, another simulated shipping study was carried out that assessed the impact of individual stress elements (shock/drop, aircraft vibration, and truck vibration) in isolation on re-dispersion time as a function of syringe orientation.

It was observed that the shock/drop stress actually reduced re-dispersion time for TD orientation (Fig. 1), especially for DP Lot 2 (where re-dispersion time reduced from 42 s to 27 s) and DP Lot 3 (where re-dispersion time reduced from 70 s to 37 s). Aircraft vibrations, on the other hand, increased re-dispersion time in the TD orientation (Fig. 2). The re-dispersion time increased from 43 s to 63 s for DP Lot 1, from 42 s to 92 s for DP Lot 2, and from 70 s to 120 s for DP Lot 3. Similar to the aircraft vibrations, truck vibrations increased re-dispersion time in TD orientation (Fig. 3). The re-dispersion time increased from 40 s to 78 s for DP Lot 1, from 52 s to 103 s for DP Lot 2, and from 65 s to 170 s for DP Lot 3. These findings are similar to aircraft vibrations although the magnitude of increase in re-dispersion time is slightly more compared with aircraft vibrations. Additionally, there was little effect of shock-drop, air, and truck vibrations on the re-dispersion time for syringes in the TH and TU orientations (Figs. 1-3).

Effect of Actual Shipping on Re-dispersion Time

Syringes shipped in controlled TH and TU orientations had re-dispersion times averaging less than 10 s, while syringes shipped in controlled TD orientation showed an increase in re-dispersion time from less than 10 s to over 60 s after the syringes were shipped over a period of 3 weeks from the manufacturing site to the testing site.