Delivering the intended drug: Adding surfactant to IV administration fluid prevents protein particles

Each year, over 12 million people are diagnosed with cancer, and many others are impacted as a family member or close friend. No matter how one is affected, cancer causes pain, heartbreak and suffering. Scientists at Bristol-Myers Squibb and other pharmaceutical companies have been working hard to develop solutions to this increasingly common disease. Despite popular belief, development of a new treatment (pharmaceutical drug) is not as easy as one might think. The discovery and development process can take years to complete; requirements are strict, detailed and difficult to meet.

Once a potential new therapy is discovered, pharmaceutical scientists must endure many obstacles along the path of delivering it to patients. One such hurdle is the clinical development process, which can be long and time-consuming. Clinical trials are designed to test whether the experimental medicines are both safe and effective for human use. Clinical trials are comprised of three distinct phases with different goals. While Phase 2 and 3 trials are critical to understand the effectiveness of a drug in different populations, dose optimization is performed during the Phase 1 trial. Dose optimization is a comprehensive strategy used in drug development to assure a drug displays maximum efficacy against a targeted disease, while ensuring an acceptable toxicity level. In other words, a dose that is unsuitably high for the patient can cause side effects, while a dose that is too low can result in either no response or a response that is too small to fully treat the patient. The potentially wide range of dosage amounts needed in the dose optimization process can be achieved by diluting the drug solution before it is administered via IV injection. Usually, normal saline or dextrose solution is used to accomplish the dilution. For example, cancer patients can have low body mass (as low as 30 kg). Dilution allows them to participate in the study and receive a potentially life-saving medication, as a smaller dose of the drug can be administered.

Biological drug products are often protein molecules. For a biological drug to be safe and effective, the proteins must remain as individual molecules. If the molecules clump together (aggregate), the drug could be rendered useless. Worse, these protein aggregates can cause an immune response or can even be toxic. Polysorbate 80 (PS-80) is a common inactive ingredient that is added to protein formulations to minimize protein aggregation. Polysorbate-80 and other surfactants are often used in foods or cosmetics, as well. Surfactants have a component that likes water (hydrophilic) and a component that “fears” water (hydrophobic). Soap is a surfactant, too; the hydrophobic component grabs on to dirt and grease, and the hydrophilic section helps carry it away in the water. In a similar way, the PS-80 interacts with the protein and helps it stay in the drug solution by preventing protein-protein interactions, which may be a cause of protein aggregation.

For example, a protein drug product that contained PS-80 was intended for use in Phase 1 trials. The drug product was confirmed to be suitable for use at 70% dilution with normal saline. The clinical trial was later expanded to lower doses, requiring much higher dilution of the drug product.

Contrary to the common belief that protein aggregates are less likely to form at lower protein concentrations, proteins were found to be clumping together in the diluted drug product. Further investigation uncovered that the extra dilution caused the PS-80 level below a certain critical level, which led to protein clumping (particle formation).

As a result of these findings, a new approach was developed that included adding PS-80 to normal saline solution prior to drug product dilution. This ensured maintenance of adequate PS-80 levels across a wider range of protein concentrations and allowing additional flexibility within the clinical trial. Reformulating a drug product with a PS-80 concentration suitable for increased dilution would have taken several months of development time, causing a significant delay in the clinical trial. The new approach should be useful for broader applications in early stage clinical trials, where there is uncertainty regarding dose levels. The FDA has approved the use of this approach, and it has proven useful in clinical trials. This new strategy will create better opportunities for patients, especially cancer patients with very low body mass that need lower doses in order to receive these potentially life-saving biologic drugs.

Acknowledgement
Authors thank Drs. Munir Hussain and Nancy Barbour for review.

Katie Yang [1]***, Songyan Zheng*** [2]***, Mary Krause*** [2] ***and Dilbir Bindra*** [2]
[1]*Montgomery Upper Middle School, 375 Burnt Hill Road, Skillman, New Jersey, USA*
[2]*Drug Product Science and Technology, Pharmaceutical Development, Research and Development, Bristol-Myers Squibb, New Brunswick, New Jersey, USA*

Publication

An Approach to Mitigate Particle Formation on the Dilution of a Monoclonal Antibody Drug Product in an IV Administration Fluid.
Zheng S, Adams M, Mantri RV.
J Pharm Sci. 2016 Mar