A key objective of pharmaceutical and biopharmaceutical development is to increase product therapeutic specificity and safety. Some of the recent exciting developments have obviously been related to the development in new chemical entities for the treatment of underserved disease populations. However, increasingly, successful developments in this field involve new formulation technologies that use engineered physicochemical attributes to enable and improve the efficacy and safety of new and existing products. These formulation technologies can positively affect product specificity, bioavailability, biodistribution, pharmacokinetics and safety. Formulation technologies can not only impact the delivery of a single therapeutic molecule but combine pharmaceuticals and biopharmaceuticals to provide uniquely new and useful product attributes and clinical applications. Two major advances in recent years have been the development of monoclonal antibody-drug conjugates (ADC) and the many forms and applications of nanoparticles.

**Antibody-Drug Conjugates**

The combining of pharmaceuticals and biopharmaceuticals in the form of ADC has been a goal of research since the advent of monoclonal antibody technologies forty years ago. This approach holds the promise of combining the beneficial attributes of drugs and the exquisite specificity of monoclonal antibodies. In oncology focused ADC for instance, cytotoxic drugs that could treat the desired disease are covalently bound to disease relevant antibodies via a chemical linker (Figure 1). Eight different human monoclonal antibodies have been approved for cancer therapy, several of which bind to cell surface tumor antigens. From this portfolio of antibody specificities, two ADC products have recently been approved as commercial clinical therapies.

ADC products must use antibodies with specificities that can bind to cell surface antigens and be subsequently internalized via endocytic vessels. The therapeutic success of ADC products depends upon the ADC construct being internalized by the tumor cells, and the linker associating the antibody to the drug being hydrolyzed by the acidic environment of the endosomes (approximately pH 5.0). Then the cytotoxic drug must maintain its ability to cross endocytic membranes, possibly with linker remnants still attached, into the cytoplasm where it can function as a therapeutic. So development of ADC technology has depended heavily on these typically proprietary linkers. However, the utility of different combinations of antibodies, linkers and drugs has been difficult to predict, which has complicated the development of new ADC products.

While the ADC pipeline is robust, there are technical limitations to what can be accomplished. Inability to significantly increase the ratio of the number of copies of cytotoxic drugs attached to targeting antibody creates dose boundaries for ADC development and limits its applicability. ADC products need a high copy number of targeted tumor antigens expressed on tumor cells to enable the needed cytotoxic dose of drug being internalized by cells, and the cytotoxic drugs used for these conjugates need to be of very high potency to minimize this necessary dose. These limitations result in only a small portion of the portfolio of therapeutic drugs being applicable to ADC.

**Nanoparticle Formulations**

There are wide variety of nanoparticle technologies used in drug delivery and they have had a major impact on formulating pharmaceuticals. These nanoparticle technologies offer a number of attractive attributes for drug delivery including: improved bioavailability, delivery of high doses, protection of the drug from harsh environments, extending pharmacokinetics, targeted biodistribution of drug, sustained release of the therapeutics, and co-delivery/combinations of pharmaceuticals.
Engineered nanoparticles, much like ADC, can “link” pharmaceutical drugs to targeting monoclonal antibodies generating highly specific therapeutics that also offers significant advantages that address the limitations and challenges faced by ADC products. Antibody targeted nanoparticles can dramatically improve the drug loading and delivery over ADC constructs. The delivery of these particles, with their high drug payloads, is no longer absolutely dependent on the target antigen copy number; as long as sufficient antibodies on the particles bind to the target antigen linking the particles to the cells, the drug contents of a particle will be delivered. This dramatic improvement in drug loading promises that drugs can be delivered to target cells with low copy number antigens. Furthermore, nanoparticle formulations, as compared to ADC formulations, can benefit from the EPR effect and do not depend on intracellular hydrolysis of a chemical linker, but rather provide therapeutic effect when either localized within tumor tissues or internalized by tumor cells.

Formulation technologies are a critical contributor to current and future improvements in pharmaceutical and biopharmaceutical development. Because of their compelling advantages, nanoparticles will see rapidly increasing adoption and use in both pharmaceutical and biopharmaceutical products. Lastly, as the biosimilar field expands and begins to improve existing biopharmaceutical products, creating “biobetters,” these formulation technologies are certain to play a leading role.

References