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Analytical Methods for Single Entity Combination Products

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The demand for sophisticated drug delivery has led to the development of many innovative combinations of pharmaceuticals, biologics and medical devices across a broad range of therapeutic areas. While these combination products have the potential to fulfill major unmet medical needs, they also present unique challenges in development and approval. One of these challenges is the development and validation of analytical methods to assess the quality, safety and stability of combination products.

Types of Combination Products

The FDA Guidance for Industry Titled "Current Good Manufacturing Practice Requirements for Combination Products (January 2017)" defines a combination product as "a product composed of two or more types of medical products (i.e. a combination of a drug, device, and/or biological product with another)." There are three types of combination products: single entity, co-packaged and cross labeled.

A single entity combination product has two or more related components (i.e. drug/device, biologic/device, drug/biologic or all three) that are physically, chemically or otherwise combined to produce a single entity. Examples of single entity combination products would be a prefilled syringes or a drug eluting stent.

A co-packaged combination product has two or more components packaged together in a single package. Examples of co-packaged combination products are surgical and first aid kits.

With a cross labeled combination product, each component is packaged separately and is intended only for use with an approved second product. An example of a cross labeled combination product would be a light activated drug requiring a light emitting device.

Single entity combination products (SECP) present unique analytical challenges compared to co-packaged and cross labeled combination devices. Most notably, a SECP runs the risk of impurities and degradants from the combining process and sterilization. In addition, an SECP may have specific design features that need to measure to ensure proper functioning of the product.

As a result of these unique analytical challenges for SECPs, this white paper will focus only on the analytical methods needed to support the development of an SECP. For brevity, this white paper will only discuss SECPs formed from a drug and a medical device. Similar approaches with the appropriate methodologies could be adapted for the other types of SECPs.

Analytical Methods for Assay, Related Substances and Degradation Products

There are three goals for these methods: to assay the drug content, to measure for known related substances and to detect degradation products of the drug. Like the analytical methods for more tradition drug products, the predominant instrumentation for these methods is high-performance liquid chromatography (HPLC)-UV, with one method usually able to accomplish all three tasks.

The main difference between analytical methods for SECPs and traditional drug product formulations like oral or parenteral dosage forms is in the sample preparation. The sample preparation is unique and specific to the SECP but usually involves complicated multi-step procedures. Based upon the SECP, sample preparations of SECPs often involve extensive extraction for complete recovery of the drugs. In addition, depending upon the size of the SECP and the location of the drug, the SECP may need to be disassembled or reproducibly cut, which can be a significant challenge when the SECP is made from hard plastics or metals.

Since the method is intended to be used as to evaluate stability of the SECP, the method will need to be proven to be stability indicating. If the SECP contains a new drug, a forced degradation study will be needed. If the SECP contains a generic drug, literature references to known degradation pathways and impurities can be used to evaluate if the method is stability indicating. However, if the combining process is significantly different from the literature references, additional degradation pathways may need to be explored experimentally.

When designing a forced degradation study for a SECP, the potential for the device to contribute to the drug degradation or to degrade itself, leading to detectable degradation products, needs to be considered. The type of SECP will determine if the forced degradation study is done on just the drug, on the fully assembled SECP or on a combination of the drug and the parts of the device with direct drug contact. It is recommended to include the components of the SECP that have direct drug contact in the forced degradation study.

The conditions of the forced degradation study may also need to be adapted for an SECP. Stress conditions can be replaced with more relevant experimental conditions with proper scientific justification.

Once developed, the analytical methods need to be validated according to the ICH Harmonized Tripartite Guideline, Validation of Analytical Procedures: Text and Methodology (ICH Q2 (R1)). One important additional consideration for validation of methods for a SECP is during ruggedness. In the ruggedness validation experiments, additional challenges should be added to evaluate ruggedness of the sample preparation. These experiments will vary depending upon the SECP and need to be appropriately challenge each critical sample preparation step.

Residual Solvents Methods for a SECP

If organic solvents are used in the assembly of the SECP, the finished SECP will need to be tested for these residual solvents. A common example would be if the drug is sprayed onto part of a medical device during the assembly of the SECP. In this case, the solvents used in the spraying process would be considered residual solvents.

The residual solvents methods need to be developed and validated in accordance with USP <467>. One important additional consideration for residual solvents for a SECP may be the need for additional sensitivity. Because these residual solvents may be important parameters in developing the process to manufacture the SECP, the methods may be needed to reach sensitivities as much as 10 fold lower than the required specification to assist in development of the manufacturing process. Once the methods have been validated, residual solvents testing can be done as part of release testing or as part of the process validation.

Analytical Method to Evaluate the Drug Release/Elution from a SECP

If the SECP is not intended to mechanically infuse the drug into the patient but instead the drug is intended to passively diffuse into the patient, then analytical methods designed to measure the rate of drug release or elution are needed. To perform this experiment, the SECP is placed in an appropriate media designed to model the target tissue. The analytical method is then used to measure the increase in drug concentration in the media over time. The instrument conditions used are usually similar to those used for the assay; however, more sensitive methods may need to be developed if the release of drug is expected to be slow. The method will need to be validated similar to an assay method with special consideration to sensitivity and additional ruggedness testing for the sample preparation factors that might impact the release rate.

Analytical Method to Evaluate Uniformity

For SECPs where the medical device is coated with a drug or drugs, the uniformity of this coating will need to be evaluated. Similar to the drug release methods, the instrument conditions used are usually those used for the assay; however, more sensitive methods may need to be developed depending upon the intended level of drug in the coating. In addition, the sample preparation will need to be adjusted so that samples are taken from all areas of the device to ensure uniformity of the coating. In some SECPs where the device is not a simple geometric shape, the surface area coated from the different sections of the device will need to be included in the determination of the level of the drug in the coating.

Analytical Methods for the Analysis of Leachables from the SECP

Leachables (a.k.a. migrants) from the medical device need to be considered when the drug is in direct contact with the medical device during the intended shelf storage, when the SECP is intended to be surgically implanted or when the SECP will have direct patient contact for an extended period of time. For these types of SECPs, two types of studies are performed. The first study is a forced extraction study on just the medical device and the second study a migration study on the entire SECP.

In a forced extraction study, the medical device is extracted with two solvents at an elevated temperature. Usually the drug is not included in the forced extraction. The extraction solvents are selected so that one mimics either the drug formulation or the intended patient tissue that the SECP will contact, and the second solvent is selected to represent a “worst-case scenario” condition based upon either the drug formulation or the intended patient tissue. The sample extracts are analyzed by mass spectrometry (gas chromatography, liquid chromatography or inductively coupled plasma (GC-MS, LC-MS and ICP-MS respectively)) to attempt to identify all possible organic and inorganic extractables.

Analytical methods are then developed that can detect the extractables observed in the forced extraction studies as leachables in either the drug product or a model solvent that mimics the intended patient tissue. Analytical methods for leachables need to be extremely sensitive and usually require MS detection. An additional challenge commonly arises when the drug product is present at concentrations significantly higher than the levels required for detection of the leachables. In this case sample preparation steps and method adaptations need to minimize the interferences from the drug. Once developed, the analytical methods need to be validated before proceeding to the migration study. The validation of the methods should be similar to validation of a method for related substances but allowances may be needed to reach the required level of sensitivity.

The migration study is the second study where the leachables (a.k.a. migrants) are monitored. When the risk of leachables is deemed to be highest from the drug being in direct contact with the medical device during the intended shelf storage, the leachables should be evaluated as part of the stability study to determine the shelf life. When the risk of leachables is due to the SECP being surgically implanted or from direct patient contact, a simulated migration study is performed. In this case the SECP is exposed to a model solvent that mimics the intended patient tissue at 37˚ C for an appropriate length of time determined by the intended use.

In both studies, previously validated analytical methods are used to evaluate the leachables entering the drug product or the model solvent.

Other Analytical Methods

Since many types of SECPs are in development with many unique critical features, analytical methods may be required to measure qualities specific to a given SECP that are expected to be critical to function properly. In this case the analytical method will need to be developed to address a specific attribute of the SECP.

These methods will still require validation even when few of the standard validation parameters apply. In this scenario, the validation should address at a minimum reproducibility and ruggedness. Ruggedness testing should include all method parameters that could impact the reported result.

Conclusion

As diverse and ingenious SECPs continue to be developed, analytical methods that can be used to support the development and ensure the quality of these products are needed. A thorough understanding of the SECP is critical to ensure that the analytical methods are monitoring the proper attributes of the SECP and the analytical chemist may need to be creative in developing methods and preparing samples to support these important therapeutic advances.

About the Author

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Kurt L. Moyer has more than 23 years of pharmaceutical development experience spanning all areas from discovery support to marketed products. His primary expertise is in the areas of bioanalysis, extractables and leachables, method development and validation, identification of impurities and metabolites, and GLP/GMP compliance. He also has extensive experience with drugs for anticoagulant and cardiovascular therapies. In addition, Dr. Moyer provides NSF Health Sciences clients with project management that is designed to accelerate the development process. Prior to joining NSF Health Sciences, Dr. Moyer served as a Senior Research Investigator for Sanofi Aventis and a Research Scientist for the DuPont Pharmaceutical Company. Dr. Moyer received his Ph.D. in biochemistry from Villanova University.

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