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The International Debate on Quality by Design Approach and Regulatory Perspective for Injectable Combination Products

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Pharmaceutical product quality is defined as a product that is contamination free and delivers the therapeutic gain consistently to the patient as promised in the labeling conditions. Quality by Design (QbD) is a systematic approach that begins with pre-defined objectives and emphasizes product and process understanding based on sound science and quality risk management. Thus, QbD requires an understanding of the influence of formulation and process variables on product quality. The unit formulation variables and critical manufacturing process variables such as mixing, aseptic filtration, filling and sealing, and terminal sterilization affect product quality of injectable combination products (CPs). Combination product is defined as a combination of two or more products that occur as a single entity or separate products that are labeled to be used together such as pre-filled syringes/autoinjectors and drug product in vial co-packaged with a syringe. The US and European regulatory agencies have published guidances to regulate combination products which are 'Principles of Pre-Market Pathways for Combinaton Products' and 'Guideline on the quality requirements for drug device combinations' respectively. The USFDA has gone to great extents to ease the CP approval after 1990 when the Safe Medical Devices Act (SMDA) introduced the concept of combination products, however EU mandanted burdensome processes for each component part of the drug-device combination (DDC) approval. EU did not have a pathway for approval of DDCs and addressed medicinal product and drug device separately. Nevertheless, EU released Medical Device Regulation (MDR) in order to replace Medical Device Directive (MDD). Recently, there has been a spike in the number of Marketing Authroization Applications (MAAs) wherein a medicinal product is combined with a medical device or its component in an integral or non-integral fashion. Integral DDCs are two or more separate components that are physically integrated during manufacturing (eg. prefilled syringes and prefilled cartridges) whereas non-integral DDCs are two or more separate components that are not physically integrated during manufacturing and have to be combined prior to the administration of medicinal product (eg. injection needles and filer needles). The chosen device for its intended use should critically account for relevant quality aspects and the consequences on Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs) and overall control strategy. The combination product has to be in compliance with current Good Manufacturing Practices (cGMP) and Quality System Regulations (QSR) for each constituent part before combination. During and after the drug deivce combination, both sets of regulatory standards would apply. As drug device combinations are comprised of more than one type of regulated component (drug, device or biologic) drug-device combinations will typically have more than one mode of action. Primary mode of action is a single mode of action that provides most important therapeutic action of the combination. FDA is required to assign a lead agency based on its primary mode of action (PMOA). For example, if the drug-device combination product's PMOA is attributable to its drug constituent part then, Center for Drug Evaluation and Research (CDER) would have primary jurisdiction, if PMOA is attributable to device constituent part then Center for Devices and Radiological Health (CDRH) would have primary jurisdiction and if the PMOA is attributable to biologic then Center for Biologics Evaluation and Research (CBER) would have primary jurisdiction.

Case Model: The catherter lock or flush solutions containing either an anticoagulant or an antimicrobial agent are intended to maintain catherter potency.

The Request for Designation (RFD) requested FDA for clarification of primary jurisdiction over these products. The device component is in compliance with the definition of device that affects either the structure or function of body in humans. However, the solution component (anticoagulant) acts by physically occupying space in the device and peventing the backflow of blood and clotting in to the catherter. Also if the solution component is an antimicrobial agent, it typically combines chemically with micro-organisms thus giving drug component a secondary role.

The physical and chemical compatibility of the medicinal product with its device/device component should be investigated throughout its use and shelf life. Microbiological attribute should demonstrate the drug-device integrity. Along with above mentioned characteristics the DDC should safely and effectively deliver medicinal product. The development of drug-device combination product should be patient centered on the aspects of therapeutic benefit as well as device performance. Self-administered CPs decrease frequent visits to physician's office, reduce costs while improving patient compliance. In order to ensure self-administration benefits, human factors studies are critical to investigate whether the device design of the delivery system and labeling instructions are acceptable. The sponsors must conduct and submit human factors studies to ensure the suitable use of DDCs. A typical human factors study comprises of risk analysis (eg. inadequate use of autoinjector reulting in missed dose or wrong dose), formative human factors study that call for modifications in labeling instructions and a human factors validation study to ensure safe use of the drug-device combination. The drug-device injectable combination product includes critical parameters, namely, usage of drug device, injectability and syringeability. Drug device combination is demanding increasing scientific alignment with drug and device regulatory authorirties for approvals. The revision of European Medical Devices Agency is in alignment with objectives of the US, but with unique compliance requirements with European Legislation. The combination product legislative requirements are distinct in different regualtory agencies, however the quality risk-based approach is similar.

Biography :

Prachi V. Atre has completed her Master's in Industrial Pharmacy Practice from St.John's University, Queens, NY, 11439. She works as a lead formulator at Medefil, Inc. on small molecule injectable liquid and lyophilized formulations. She has published poster abstracts and presentations at Anuual Meetings and Expositions such as American Asociation of Pharmaceutical Scientists (AAPS) and Controlled Release Society (CRS). She is an abstract reviewer at AAPS and has received certificates from the USFDA for 'Overview of Generic Drugs' and 'The Drug Review Process'.

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