Generic Metoprolol Succinate ER Tablet Drug Product Lifecycle
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Purpose
This study aims to provide a regulatory perspective focusing on the lifecycle of generic Metoprolol Succinate ER tablets, from pre-approval to post marketing stages, in order to facilitate regulatory assessment and help industry to bring a high quality generic product to the public.

Methods
The pre-approval and post-marketing data of Metoprolol Succinate ER tablets were surveyed and analyzed based on the information of submitted Abbreviated New Drug Applications (ANDAs) for Metoprolol Succinate ER tablets. Quality related deficiencies identified through the drug product lifecycle were analyzed as well.

Results
At the pre-approval stage, around 15% of the ANDAs were withdrawn by the applicants before the original application reached final approval stage; around 26% of the ANDAs received complete response (CR) letters from the Agency and many related to major deficiencies, which imply significant quality issues of these ANDA at pre-approval stage. Lack of in-process control is one of the major deficiencies issued from the Agency from a product quality perspective.

At post-marketing stage, compared to an average of ~10% prior approval supplement (PAS) submissions for regular drug products, PAS took around 23% of all post-approval supplements for metoprolol ER tablets. Around 50% of the PAS were approved while 43% were withdrawn, indicating high risks associated with this drug product at post-approval changes.

The survey identified main CMC related deficiencies at pre-approval stage and proposed post-approval CMC changes at post marketing stage related to drug product quality of Metoprolol Succinate ER tablets.

Conclusion
A high-quality drug product relies on in-depth understanding of product and manufacturing process, as well as an effective regulatory assessment, especially for a complex drug product like Metoprolol Succinate Extended-Release (ER) tablets. The manufacturing of Metoprolol extended release tablets using drug and polymer coated pellets is considered to be a complex process requiring sufficient in-process controls to ensure the quality of the drug product. Due to the complexity of the manufacturing process, several generic companies recalled their products of Metoprolol ER tablet in the past few years. Generic products make up about 80% of the U.S market. Large scale recalls can result in drug shortage. Ever since, both pharmaceutical industry and regulatory agency have put enormous effort to enhance parity between the innovator product and generic drug products and have brought safe and effective generic Metoprolol Succinate ER tablets with consistent quality drug product over its lifecycle to the public.