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Drug Discovery to Pharmaceutical Developing Industry

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Abstract: *The driving motivation for the search of a new drug is a new disease or unmet clinical condition. Drug discovery is a expensive and difficult process which involves identifying drug responsive to a selective unestablished target. Solid State properties, X-ray Crystallography, Mixture Analysis and Spectrometry are used to monitor the modification of target after application of a new drug molecule and quality performance is measured. This leads to further optimization and selection of a molecule for the selected target. Post discovery, Regulations and Approvals through Drug Discovery a Pharmaceutical Development is achieved, here a review is done.*

Key Word: *Drug discovery, New drug molecule, Target validation, Compound screening, Pharmaceutical development.*

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I. Brief Introduction to Pharmaceutical Development

Drug discovery is a complex and expensive process. A short review is done on drug discovery and existing pharmaceutical developing industry. The initial academic research is done to develop a hypothesis, and there is a need of data to establish a selective target. Data mining can be used for target identification. Target can be a variety of biological entities such as proteins, RNA etc. The target chosen must be accessible via a drug. The relation between target and disease must be appropriately made by observing the change in bio-molecule as the change in bio-molecule structure results in a physiological change. Target validation is the next step. It involves evaluating the response of bio-molecule at various levels starting from molecular level to physiological level. It can also be measured both *in vivo* and *in vitro*. Monoclonal antibodies validate the target. Chemical genomics i.e. the study of genomic responses to chemical compounds can be used for rapid target identification and target validation. It provides the chemical tools to have increased clarity about cellular functions prior to complete target validation. However, a multi-validation approach must be used to have increased confidence in target. Following target validation, compound screening assays are developed which confirm the modification of target i.e. a change in bio-molecular structure. Assay format is decided on the basis of the desired target, its pharmacological relevance, effects of various compounds in assay, quality, reproducibility and cost. A prospective molecule becomes a hit molecule after its action is confirmed in screening. Developing a High Throughput Screening (HTS) assay is a very time consuming process. But it being an automated process is preferred as it checks the action of entire library of prospective compound against the target identified. HTS must be performed at three levels i.e. at molecular level, at cellular level and at animal level[8,9,10]. Computer assisted analysis may be used to reduce the number of chemical compounds to be screened. High hit rate of HTS assay confirms the action of the drug molecule at the target site. As per the industry standards, assay quality is determined by Z'[11] factor. A Z' factor of an assay greater than 0.4 is considered robust for compound screening. The assay quality can also be maintained by minimizing wash steps, plate to plate reagent transfers, use of stable reagents and optimal instrumentation control. Other Quality control may also be adopted for optimal assay performance. Nuclear Magnetic Resonance (NMR) is a structure determining technique. It looks for the hits which confirm the presence of action by the prospective molecule. *In vitro* and *in vivo* mechanisms are performed sequentially to confirm the hit. Secondary assays confirm the site of action. The assay reproducibility, cost and quality is an important step which paves the way for progression in discovery of a new molecule. This new molecule is referred as a development candidate, which if successful is marketed as medicine. Recent advances in structural biology and computer technology has resulted in Computer Aided Drug Design (CADD). In this the structure of target is determined by NMR or X-ray crystallography. Virtual screening, docking techniques and library design help in discovering the drug. Further formulation development, process development nd a control strategy is established. There may be various factors which affect the drug discovery such as screening facility availability, drug design software, drug development facility. Ligands are the compounds that are recognized by the target and bind to it. The medicine that is administered is more than a molecule. Absorption, Distribution, Metabolism and Excretion (ADME) properties are also crucial for ruling in or out a drug molecule. Most of the drug molecules are administered as salts. Salt formation allows for

optimization of physical and chemical properties. Salts can exist in various crystalline forms. The parameters of the salt such as solubility, physical stability, chemical stability, hygroscopicity, dissolution, and processibility play an important role in the salt selection process.

II. Mixture Analysis

Mixture analysis allows us to quantify an unknown material in comparison with a known material. Material characterization techniques play a significant role in the determination of the composition and phase purity of various ingredients to have confirmed action at the target site. Few of the methodologies used for doing quantitative analysis of mixtures are sample preparation, data collection which leads to comparison with calibration standards i.e. comparison with known samples. This helps in quantitative analysis of unknown samples. The quantitative analysis of mixture method leads to the evaluation of specificity, precision, accuracy, robustness. The use of analytical techniques as Raman spectroscopy, near infrared (NIR) allows real-time process monitoring and control which is crucial for drug development.

III. Physical Stability

The physical and chemical stability are essential for performance and ease in processing and manufacturing the drug. Physical instabilities of the drug being developed for modification at the target site must be thoroughly investigated prior to being administered. Thermodynamic stability of the crystalline forms must be investigated prior to selecting a stable form. Physical instabilities such as change in crystalline structure, loss of crystalline structure, phase transformations, melting, dehydration and hydration of salt may lead to changes in nature of crystalline order, particle size, and morphology. These physical instabilities initiate a pharmaceutical interest to constantly improve until a physically stable drug product is achieved.

IV. Chemical Stability

Chemical instability such as degradation of drug, change in appearance, disorder of crystals can be catastrophic as it can sometimes lead to loss of healing potential of the drug molecule. Chemical instability can also lead to formation of toxic compounds upon degradation. The development of partial amorphous structure can lead to accelerated chemical reactivity at the target site. The disorder of crystal defects such as partial amorphous structure also enhances the solid state chemical reactivity. Thus, the ionizable compound selected as salt for action at the target site must be chemically stable to have the desired therapeutic response at the target site.

V. Quality by Design

It is a continuous learning process. It involves formulation of quality strategies and selection of appropriate manufacturing processes which can consistently deliver the intended performance of the drug product. The drug product must be carefully designed to meet patient requirements. The factors which cause process variability are identified and controlled. This variability is continuously monitored to ensure the desired performance of the drug product and to ensure consistency in quality over the time. Quality of performance can be achieved by Quality by Design. Risk analysis and management in Quality of Design is an important step. It considers the various potential risks to the performance by measurement of uncertainty, identify the problem and implementing the solution. By doing careful experimentation, drug product development by Quality of Design can be done correctly in the first time. This leads to reduction in the time to market the developed pharmaceutical drug.

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