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RECENT TRENDS IN PHARMACUETICAL REVERSE ENGINEERING

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ABSTRACT

According to the definition established by the FDA, a generic drug is "a drug product which is comparable to a reference listed drug (RLD) product in dosage form, strength, route of administration, quality, performance characteristics, and intended use". Rigorous rules and regulations pertaining to abbreviated new drug application (ANDA) submissions are complex and the generic drug industry strives to meet these regulations to obtain FDA's approval. And being the "first to file" is the most fundamental principle in the generics business because several companies compete to create generics of successful products going off patent. Therefore, generics companies must be highly skilled and disciplined in product development and achieving bioequivalence—the most critical development area.

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INTRODUCTION

Though generics companies commonly use reverse engineering techniques, the topic and, more importantly, the tools needed to carry out the process are rarely discussed in the public domain. In this application note we discuss one such tool that can be used for oral solid dose formulations Two cold remedy formulations were analysed on the Morphology G3-ID: one was a commercial brand and the other a generic one. Individual components within the formulations were identified by comparing their Raman spectra with those in a commercial database. Once the components were identified the particle size distributions of individual components in each formulation were compared, as was the overall composition of the two formulations.

The cold remedies were dry powder formulations that were automatically dispersed and analysed using the Morphology G3-ID. 13 mm3 of sample was dispersed using the instrument's integrated dry powder dispersion unit using the low pressure dispersion option.[1]

The samples were morphologically analysed using the 5 x objective. Particles with a circular equivalent diameter (CED) larger than 25µm were targeted for the Raman chemical identification.

In this case the acquisition time was 10 seconds for each particle and spectra from a few thousand particles from each sample were gathered in an overnight analysis.[2]

REVERSE ENGINEERING OF PHARMACEUTICAL FORMULATIONS MAY BE REQUIRED FOR A VARIETY OF REASONS:

- Intellectual property issues (viz. patent infringement)
- Analytical issues (viz. matrix extraction)
- Stability issues
- Safety issues
- Generic formulation design and development

Reverse engineering of a formulation can be done using public domain information about the composition of a drug product, and applying knowledge and experience of formulation science to develop an approximation to the quantitative formula and likely manufacturing process.[2]

It is possible to estimate the quantitative formulation from the qualitative formulation using the knowledge and understanding of:

- Formulation science.
- The implications of chemical structure for the stability of the API.
- Excipients; understanding their function, their limitations, and typical levels of use.
- Pharmaceutical unit processes.
- How these different facets of the product interact with each other.

Reverse engineering at this level is not an exact process but provides a reasonable estimate.

Finn Brit consulting has many years of practical experience of reverse engineering of pharmaceutical formulations and can assist with such work.[3]

PHARMACEUTICAL REVERSE ENGINEERING:

Reverse engineering is methods that is used in re-produce and re-design an existing product. By using this method, the design of product can be study and improve produce. The purpose of this method to increase the product capability. This project related with redesign and analyzes the mold for a bottle pack cap at in Medicare. To produce the mold, measurement must be taken at the product, and from the measurement the product can be draw in the 3D model. The product will be measured by using suitable equipment. The filling simulation process by using mold flow Express is used to analyze the design. Then, the design of the core and cavity of the product is finalized. The process flow started with indentifying the part following with measuring the dimensions at the product and the end was simulating the filling process on the mold by using simulations.[3, 4]

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THE ROLE OF REVERSE ENGINEERING IN THE DEVELOPMENT OF GENERIC FORMULATIONS:

The first to gain the most is a fundamental principle in the generics business because several companies compete to create generics of successful products going off patent. For a generics company to maintain revenue growth in a market in which product prices continue to fall, it must secure a continuous flow of new products, with quality and speed to market being key drivers. Thus, generics companies must be highly skilled in product and process development.

The generics business and achieving bioequivalence the most critical development area. Most generics are oral solid dosage forms (e.g., tablets and capsules) that are composed of various excipients, each having a specific purpose.[5]

Although excipients are clinically inactive, they are pharmaceutically active and, therefore, can affect all aspects of drug product performance.

For example, functional excipients such as stabilizers and dissolution modifiers contribute to the dissolution and bioavailability of drug products. Determining the original drug's excipient content and other formulation optimization steps can be facilitated using reverse engineering, which is the decoding of an innovator product's formulation parameters. Such parameters include the quantitative composition of the innovator product, the solid-state characterization of the active pharmaceutical ingredient (API), and the manufacturing process.[5, 6]

Although some information about an innovator drug product's API and excipient components can be found in common sources such as product information brochures, Physician's Desk Reference, or FDA's Web site (http://www.fda.gov/), one can be more confident about the generic product's performance by developing a formula that is as qualitatively and quantitatively similar to the reference listed drug (RLD) as possible. Under US law, quantitative information about the excipients in oral dosage forms is not required to be revealed. In this context, reverse engineering of the innovator product's formulation is a scientifically sound and cost-effective strategy for accelerating generic product development. From a practical perspective, the chances of developing a bioequivalent product can be significantly increased by extending the concept of generic product sameness to formulation sameness with the RLD. Generic product sameness is defined in terms of pharmaceutical equivalence and bioequivalence. Formulation sameness with the RLD is defined in terms of equivalence of qualitative and quantitative formulas, solid state characteristics, and manufacturing process to the RLD.

Though generics companies have used reverse engineering for quite some time, the topic is scarcely covered in the published literature. In this article, we discuss the importance of reverse engineering and propose a decision-making process for developing solid oral dosage forms.

We suggest various components of reverse engineering and the tools needed to carry out the process. The method is based on information generated from a series of reverse engineering experiments on RLD products.[6]

COMPONENTS OF REVERSE ENGINEERING

Decoding the quantitative formula.

Decoding an RLD's quantitative formula should begin with identifying which excipients most affect the formulation's performance in quality tests (i.e., stability or dissolution). These data will provide information about the resources required for reverse engineering versus the importance of the information derived. Resources (e.g., time and money) can be streamlined on the basis of these findings because sometimes traditional formulation optimization techniques may be more efficient than reverse engineering. In general, pH-adjusting agents, buffers, stabilizers (e.g., antioxidants and chelating agents), and dissolution modifiers (e.g., surface active agents) are the best candidates for reverse engineering.[6, 7]

The next step is to quantify an identified excipient in the tablet matrix, which is challenging because of possible interference from the other excipients. Hence, the excipient must first be separated from the tablet matrix using techniques such as differential solubility, filtration (with filters of a specific pore size or molecular weight cutoff), high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), and size-exclusion chromatography. One must select the separation technique based on the number of interfering components present and their physicochemical properties.[7]

SCOPE AND IMPORTANCE

This is the main purpose that will be study. From the reverse engineering process, to produce the new pattern of the product it must apply the injection molding process the injection molding process is use to produce the bottle pack cap by making the core and cavity of the product before this. To making the reverse engineering product, it must follow the first step until the last step in the reverse engineering process. Reverse engineering process is a unique technique that uses the existing entity information to produce a new entity that has some of same properties of the existing entity.

Reverse engineering of a formulation can be made by means of public province information about the symphony of a drug product, and applying acquaintance and knowledge of formulation discipline to increase an approximation to the quantitative formula and likely manufacturing process.It is attainable to assessment the quantitative formulation from the qualitative formulation using the information and understanding of:

•Formulation science.
•The repercussion of chemical structure for the stability of the API.
•Excipients; understanding their function, their restrictions, and their levels of use.
•Pharmaceutical unit processes.
•How these different facets of the product interact with each other.[7, 8]

MARKETANALYSIS

An overview of the global market for generic drugs, including coverage of therapeutics such as antibacterial, antidepressants, anticancer agents, anti-arthritics, cardiovascular drugs (e.g., hypolipidaemics and antihypertensive), and drugs for respiratory conditions, including asthma and COPD. The global generics sector reached $269.8 billion in 2012. This sector is expected to reach $300.9 billion in 2013 and $518.5 billion in 2018, with a compound annual growth rate (CAGR) of 11.5%.Analyses of global market trends, with data from 2012, estimates for 2013, and projections of compound annual growth rates (CAGRs) through 2018.[8]

REVERSE ENGINEER A PHARMACEUTICAL PRODUCT:

Application for generic approval under ANDA requires the demonstration of a bioequivalent product. This means that the blood levels of the active ingredient need to track those of the innovator's product over the time frame from ingestion to absorption. The simplest way to ensure this is often to mirror the innovator's formulation so that the dissolution profiles are identical. For the case of biosimilars, mere bioequivalence is not enough and the product must be highly similar in composition. Despite this registration requirement, the FDA will not divulge the innovator's formula as it is proprietary, leaving the generic manufacturer to figure it out through their own means, or have the application denied.[8]

DIFFICULT IS REVERSE ENGINEERING A PHARMACEUTICAL:

While this may not seem very complicated, performing this in a laboratory can be very time consuming and complex. In order to properly deformulate a product to reveal its true base components one first has to separate out the components of the formulation before traditional analytical techniques can be used. Because some products matrices do not cleanly separate, the quantitation of ingredients, once identified, can also require specialized knowledge and advanced instrumentation to perform.

Some products are easier to deformulate than others depending on how many ingredients are within the product, levels, and product form. For example, a controlled release formulation will require not only chemical analysis of the contents, but an elucidation of the CR mechanism.[9]

LEVELS OF PHARMACEUTICAL REVERSE ENGINEERING ARE AVAILABLE:

1st Level Deformulation–

Identifies and quantifies the major ingredients. Typically quantitation is not performed. This is often used to verify label claims and/or give guidance to the formulation chemist.

2nd Level Deformulation–

Identifies and quantitates all components of the formulation down to coloring/taste masking agents, the CR, and the coating systems for tablets.[10]

3rd Level Deformulation–

Everything in the first and 2nd level, as well as identification and quantitation of all impurities and process markers in the system which is needed to ensure the ANDA will meet with approval with consideration to ICH Q3B (R2), impurities in New Drug Products.

(FTIR) Fourier Transform Infrared Spectroscopy–

All ingredients within a formulation are represented in an FTIR spectrum, which is then analyzed against known libraries. While this gives a great starting point using a FTIR is primarily only useful for the major ingredients within a formulation, as ingredients that are at very low levels may not appear.

(TGA)Thermogravimetric Analyzer–

Samples are decomposed through a heating process. While additives and organic material will be burned away during this process, inorganic fillers will remain. This process is commonly used to quantify the amount of residue and resin that are inside of a sample. Based on decomposition temperatures clues to the composition of information can be obtained which can help direct which other instrumentation will be used next.

(Pyro GC/MS) Pyrolysis Gas Chromatography/ Mass Spectroscopy–

This technique also decomposes a sample. Once decomposed a gas chromatograph can separate out the components in order to allow them to be identified using mass spectroscopy.[11]

(FID) Flame Ionization Detector–

A FID is a universal detector that can help further quantify ingredients within a sample. Using this along with traditional methods of separating the solvents and then identifying/ quantifying them using GC/MS can lead to further knowledge of a samples composition.

Karl Fisher–

An Instrument that is used to identify the amount of water that is within a sample.

(SEM/EDXA) Scanning Electron Microscope/Energy Dispersive X-Ray–

Ash residue can be analyzed utilizing this instrumentation in an effort to determine the types of elements that are present within a product sample. This provides information about inorganic excipients.

(XRD) X-Ray Diffraction–

Useful for the determination of polymorphs in a drug product.[11, 12]

Deformulation Services for Pharmaceuticals.

Pharmaceutical deformulation can be used for:

- Competitive product characterization.
- Development of generic drug products.
- Identification of batch to batch variations.
- Comparative analysis of "good" and "bad" samples.
- Patent infringement or trade secret investigations.[13]
- Deformulation involves instrumental techniques and conventional extraction methods to identify and quantify the components of a complex mixture. Although we do not guarantee a "cookbook recipe", our analysis in most instances identifies the chemical class of major and minor components. A computer library search is also performed when needed to locate the trade names of similar, commercially-available materials.
- Our experienced chemists are kept up-to-date with the latest methods and have developed techniques for unraveling complicated formulations.[14]

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