

In the Details

The appearance of any packaging solution is driven by a variety of factors, the most significant of which have a direct impact on the safety and usability of a product. On top of this, commercial motivations must also be taken into account, so the final design must strike a balance between a surprisingly wide range of considerations

Packaging can be a major factor in what brings a product to life. With the ever-increasing expansion of the pharmaceutical industry, there is continuous pressure for biopharmaceutical companies to develop and launch new drug products. Coupled with the increasing number of drug products coming off patent, greater importance is being placed on the use of packaging for product differentiation. Packaging is therefore fast becoming one of the most important considerations in the growth and success of any drug product. This is evident from the global healthcare packaging component market being currently valued at \$87.3 billion (£54.6 billion) (1).

Function of Packaging

Packaging can be considered from various aspects, but for many within the pharmaceutical industry, its main purposes are:

- Communication, without confusion, of important product information, such as dosage strength and directions for use
- Containment of the drug product
- Protection of the drug product from external elements
- Facilitation of product storage and shipment
- Distinction of a product from competitors

Lockhart in 1997 summarised the functions of packaging in a tool referred to as 'The Packaging Matrix' (see Table 1, page 26) (2). Traditionally, the packaging of drug products was viewed as a method of enclosing, branding and protecting finished products for distribution, storage, sale and use. Times

have changed however, and product packaging design now has the potential to impact consumer buying decisions.

Pharmaceutical companies are beginning to recognise the importance of packaging design, with significant time and resources being allocated to research and development in order to understand the consumer's perception of a product. Based on these findings, pack presentations are being created to 'talk' directly to the end-user.

Pharmaceutical packaging design should reflect the changes in market dynamics. Historically, packaging was relatively simple and plain, and it was common for similar packaging to be used for different drug types and this, coupled with only text and colour differences, often caused confusion as the product was not easily recognisable. Packaging design today encompasses all the key areas identified in the packaging matrix in Table 1, but several factors have had a major influence on current packaging design trends.

Factors Influencing Packaging Design

The factors to consider when deciding on the design of a pharmaceutical product's packaging can be grouped into several categories.

Regulatory Guidelines

The aesthetic design of the drug product packaging is not stipulated in any regulation. This is very much up to the individual pharmaceutical company, but in Europe, regulations covering critical packaging, labelling and patient information leaflets data requirements are set out in Directive 2001/83/EC. The MHRA 'Best Practice Guidance on

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Labelling & Packaging of Medicines', issued in 2007, provides guidance to pharmaceutical companies and their dedicated packaging design teams on the key elements that will be examined upon regulatory submission, and defines critical information, such as (3):

- Name of the medicine
- Expression of strength (where relevant)
- Route of administration
- Posology (dosages of medicines and drugs)

Adhering to these guidelines and regulations facilitates the approval process but also, and more importantly, reduces the percentage of errors involved in dispensing, administering and interpreting packaging instructions.

Patient Compliance

The World Health Organization (WHO) reports that only about 50 per cent of patients take their drugs as prescribed – in other words, taking the correct dose at the correct time – meaning that half of the patient population do not. This presents a major obstacle for pharmaceutical companies and makes the delivery of healthcare difficult. In order to address non-compliance, the pharmaceutical industry has been focusing on the design of the drug product packaging, making visual compliance as clear and as simple as possible. Convenience blister packs are designed to remind patients to take medications correctly and on

Table 1: The Packaging Matrix		PACKAGING FUNCTIONS		
ENVIRONMENTS		Protection	Utility	Communications
	Human	<ul style="list-style-type: none"> • Tamper-evident features • Child-resistance features • Designs that do not require scissors or knives to open 	<ul style="list-style-type: none"> • Reclosable designs • Easy to open designs • Pre-measured units • Compliance packaging (packaging, that, by nature of its design, helps people comply with medication regimens) • Talking packages • Material • Shape • Configuration • Texture 	<ul style="list-style-type: none"> • Brand name • Warnings • Directions • Expiration dates • Storage information • Graphics • Material • Shape • Colour • Configuration • Texture • Photographs • Text
	Biospheric	<ul style="list-style-type: none"> • Amber colour to protect from UV damage • UV absorbers to protect from UV damage • Water vapour barriers • Oxygen barriers to protect from oxidation • Oxygen absorbers to protect from oxidation • Antimicrobial films to retard microbial degradation • Water vapour barrier to protect from moisture loss or gain • Wet strength corrugated 	<ul style="list-style-type: none"> • Controlled atmosphere packaging • Modified atmosphere packaging • Edible films • Wet strength corrugated 	<ul style="list-style-type: none"> • Time and temperature indicators • Pictorials
	Physical (distribution channels)	<ul style="list-style-type: none"> • Cushioning • Shipping containers • Corner posts • Airbags • Materials with adequate compression strength to withstand stacking 	<ul style="list-style-type: none"> • Stretch wrap • Shrink wrap • Self-heating packages • Self-cooling packages • Freezer to oven capable • Handles for carrying • Appropriately sized cases 	<ul style="list-style-type: none"> • 'This side up' • 'Fragile' • Barcodes • Radio frequency identification • 'Handle with care' • 'Temperature not to exceed 70°F' • Pictorials • Accelerometers

time, reducing patient medication omissions and errors, and enhancing the treatment outcomes of those medications.

An example of a pack design that encourages compliance is ZacPac – a combination treatment for *Helicobacter pylori* by Nycomed. The pack contains a small detailed booklet, replacing the ordinary patient information leaflet, providing a concise explanation of the condition and the treatment in uncomplicated words, complying with all regulatory requirements. It was the HCPC Europe Packaging Award Winner in 2007.

This triple therapy pack combines the three drug products for the twice daily treatment into one single blister, providing clear visualisation of compliance. Simultaneously, the innovative packaging design of the outer carton also aids compliance providing the seven day treatment in one carton with a clear visualisation window (see Figure 1).

The amount of money lost through people not taking their medicine

properly means that compliance features, that make it easier for patients to take the correct dosage, are also on the wish list of many customers. This is especially true for the ageing population to ensure accessibility for older people and inaccessibility for children.

Age-Related Packaging

One of the major challenges, and one which is highly important to pharmaceutical companies, is to ensure the pack design of their drug product is correct by enabling or restricting access to their product. Child-resistant and senior friendly packaging of a drug product needs to be considered within the initial discussions of a new packaging design concept, to prevent accidental poisoning of young children, while also allowing easy access for senior consumers. To determine the effectiveness of the

age-related packaging, standard industry tests are completed.

The US Federal Government has implemented various laws to ensure that materials deemed by the government to be dangerous, are packaged in child-resistant packaging. Specifically, the Federal Government enacted the Poison Prevention Act (PPA) on 30th December, 1970. The Act requires harmful substances to be packaged in child-resistant packaging such that children under five years of age, having no physical or mental handicaps, cannot “open or obtain a



Figure 1: ZacPac – triple therapy pack

Image: <http://www.hcpc-europe.org/copenhagen/pdf/klatt.pdf>

harmful amount of the substance contained therein within a reasonable time" and senior-friendly packaging must "not [be] difficult for normal adults to use properly."

Notably, the PPA does not require that children be prevented from opening or obtaining a toxic or harmful amount of the substance 100 per cent of the times attempted. When the substance is packaged in individual units, the Code of Federal Regulations requires that child-resistant packaging is effective no less than 80 out of every 100 attempts (4). Conversely, senior adults between ages 50 and 70, having no mental or physical disabilities, should be able to open the packaging no less than 90 out of every 100 attempts when permitted to view printed instructions that accompany the packaging (5).

To ensure compliance with the aforementioned federal guidelines, blister card packaging is submitted to a testing agency, which determines its child-resistance rating and whether or not the packaging is senior-friendly. Packaging is rated as senior-friendly based solely on the 90 per cent guideline, therefore, senior adults are able to open the packaging at least 90 times out of every 100 attempts. However, the child resistance rating is determined on a scale ranging from F1 through F8. The F represents 'fatal at' and the following number represents the number of doses; therefore, F4 is 'fatal at four doses'.

The more difficult it is for a child to access a product contained within a blister card package, the lower the child-resistance rating applied to the packaging. It is intuitive that products contained within packaging rated at F1, meaning it is lethal at one dose, should be very difficult for children to access; whereas, products rated at F8, meaning lethal at eight doses, do not require the same level of difficulty. However, when the lethal dose of a drug has not been established, federal regulations require an assumption that the drug is lethal at eight doses, therefore, such a drug may be distributed in packaging rated F8.

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Anti-Counterfeiting Measures

A WHO report in 2003 stated that "the United States Food and Drug Administration (FDA) estimates that counterfeits make up more than 10 per cent of the global medicines market...these figures place the annual earnings from the sales of counterfeit and substandard medicines at over \$32 billion globally" (6).

To ensure medicines are safe, effective and of good quality in order to produce the desired effect, pharmaceutical companies and contract manufacturing service providers are examining the various anti-counterfeiting technologies that can be used to help combat the growing increase in counterfeit drugs. These anti-counterfeiting measures range from overt holograms or watermarks, to covert UV and IR reflecting inks, to more advanced techniques of bio-security and RFID. Today, pharmaceutical companies can also use 'state-of-the-art' DNA anti-counterfeiting technologies; for example, forensic taggants and DNA markers.

Forensic taggants are invisible, security features that can be authenticated only by advanced reading systems or laboratory analysis. The use of nanoparticles, which may be embedded in packaging substrates or prints, generally consist of inert materials, very thin aluminum particles or rare particles with a size of between 20 and 40µm. The taggants carry customer-specific colour codes, engravings or may be mixed in a special way so that they can be uniquely identified.

DNA markers are usually printed in a defined area. Based on the key-and-lock system, a second testing liquid is used to authenticate the product. When the customised DNA pen applies the identifying liquid substance on the printed area either a colour change or luminescent reaction proves the authenticity.

In addition to the physical anti-counterfeiting methods applied to product packaging, the traceability of

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“ Some manufacturers are already using encrypted serial codes to allow authentication of their medical products anywhere in the world via the internet. For this application, each product carries a unique and highly complex security code ”

drugs is fast becoming a vital element in securing the pharmaceutical supply chain. The solution that a pharmaceutical company deploys however, will depend on the country specific market for the drug product as the requirements vary globally. The market variances in anti-counterfeiting requirements have been the cause of much debate throughout the industry and have had a significant impact on the packaging design.

For example, in 2004 the FDA released a counterfeit drug taskforce report and suggested a multi-layered approach to securing products and packaging by using appropriate technology and serialisation to monitor the movement of drugs through the supply chain. Today, the US FDA currently requires a barcode identifier of the manufacturer and product on the lowest level of packaging for prescription drugs.

In Europe however, the use of Datamatrix was recommended by The European Federation of Pharmaceutical Industries and Associations (EFPIA) to establish a single European symbology for medications as an anti-counterfeiting measure and also for identification purposes. The Association of Pharmaceutical Full-Line Wholesalers (GIRP) has also recommended the use of a Datamatrix code.

At the Global Forum of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) of the WHO in February 2011 in Singapore, the participants from international regulatory authorities and manufacturers recommended a global standardisation and serialisation syntax including country code, issuing

authorities, manufacturer's product code and a unique serial number.

Some countries, Turkey for example, have already implemented serialisation. The Turkish Ministry of Health decided that the optimum data carrier for the unique serial number, the global trade identification number (GTIN) and the batch and expiry details, is the two-dimensional matrix. This allows the product to be tracked throughout the supply chain.

Some manufacturers are already using encrypted serial codes to allow authentication of their medical products anywhere in the world via the internet. For this application, each product carries a unique and highly complex security code. The consumer or dispensing person enters the printed code on the brand owner's website or calls a hotline. If a true code is entered, the system confirms the authenticity, while a false code (suggesting the presence of a fake product) will prompt a warning message on the screen. The system logs each product query and rejects multiple entries of the same code at pre-defined levels. Should unauthorised multiple queries be made, this would indicate trafficking of counterfeit pharmaceuticals.

Conclusion

With an ever-increasing need for updated packaging technologies, and the need to ensure the security and integrity of the product throughout the supply chain,

the importance of pharmaceutical packaging has taken on a whole new significance. These advances in packaging technology, demanded by the industry, will come at a cost, which will ultimately be reflected in the cost to the consumer. These requirements and associated costs should be considered as part of every product development strategy.

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About the Author



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