Lifecaps News

The Product - A Rising Star of the Marketing Mix

Issue #2 - May 2008

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Contents

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- Pharmtech, Moscow, Russia, November 25-28, 2008

Armand van de Putte
Sr. Director Sales, Marketing and Business Development Europe, Middle East and Africa

Dear Reader,

It is my pleasure to welcome you to this new edition of the Capsugel Lifecaps newsletter. At Capsugel our aim is to help our customers to maximise commercial opportunities for their future and existing products by constantly striving to develop new, innovative dosage forms.

In this newsletter, we consider the forgotten "P" of the marketing mix: The Product. We look at patient perceptions of their medication; the role of packaging in relation to patient compliance; how increased patient awareness may influence doctors' prescribing decisions; and how extending the product range whilst maintaining patient loyalty is an important part of lifecycle management.

Consideration of each element of the Marketing Mix (product, price, place and promotion) is vital for the success of the brand. Even for the pharmaceutical industry where the prescriber is not the "consumer" and the patient is not necessarily the "payer", the same basic marketing principles apply. However, often the key role that the product itself can play is underestimated.

The Product is a marketing tool in its own right that can be used in a positive way by the manufacturer as part of the promotional activities. In Europe where companies are not allowed to advertise prescription medicines to patients, the patient's perception of their medication comes from their physical experience of handling the pack and dosage form (usually the tablet or capsule), as well as their response to treatment.

Patient recognition is important for building brand awareness and brand fidelity. This can be achieved by the strategic use of colour, shape and imprinting on the dosage form and also by the way in which the product is packaged. Clear, strong branding in terms of logos, colours and overall pack design assists patients in identifying and differentiating pharmaceutical products.

It is clear that to increase the impact of their marketing effort pharmaceutical companies should consider the opportunities offered by the Product itself, as well as on the other three 'Ps' in the marketing mix. This issue of Lifecaps Newsletter looks in more detail at how this product potential can be maximised.

Best regards,
Armand van de Putte

The Evolution of the Patient to Key Consumer

Dr. Günter Umbach, Healthcare Marketing, Dr. Umbach & Partner and Dr. Ottmar L. Mergel, OTC Top Consulting

A Changing Marketplace

In the 21st century, the pharmaceutical industry, like many other industries, has had to adapt its products, marketing strategy and communications to meet the requirements of well informed and more demanding customers. In the healthcare market, there has been a significant change in the relative importance of the prescriber, patient and payer for prescription drugs. This is particularly true for the primary care setting*.

In the past, pharmaceutical companies would research and develop new drugs, then market them to doctors who would, in turn, prescribe them for their patients. The patient had only a minimal say in the choice of medication.

Today, because of the availability of information via the internet and other visual or printed media, patients are often extremely well educated about their medical conditions and the treatment options open to them.

The E-health trend

On-line channels, such as disease-focused websites, are frequently consulted, even by older patients who are adept with the internet. Forums such as message boards, chat rooms and blogs allow patients to share information and experiences with others. People discuss their treatment and recommend certain medications, which may or may not be appropriate.

This trend towards E-health has transformed patients into consumers of health information, as well as of drugs. They are seeking active involvement in decisions related to their own health and feel better equipped to discuss and possibly challenge their doctors' opinions regarding their diagnosis and medication options.

Economic pressures

Patients today can influence which drugs are prescribed for them and so they have become a new customer target for the pharmaceutical industry. Physicians listen to their patients and are aware of any concerns they have about their medication in terms of efficacy, side-effects and handling. A doctor may be alter his/her prescribing in response to specific patient requests.

However, other stakeholders, such as insurance companies and government bodies, also play an important role. They are the "payers" whose main concern is to ensure value for money in healthcare supply and they have the power to introduce initiatives to curb spending. Automatic generic substitution, where the pharmacist replaces a prescribed brand with a cheaper generic, has been introduced recently in many

European countries. It is estimated that this policy has saved at least 20% of public expenditure per annum on medicines[1].

In countries where people with little or no private insurance have to rely on state healthcare, it is less likely that they will be receive the latest advances. This could mean a less effective treatment or result in lack of compliance because of more complicated dosing schedules leading to treatment failure. In Germany, patients know that they will only receive the most basic treatment from the GKV (state health insurance), they discuss possible alternatives with their doctors and pharmacists to decide whether they would prefer to pay for a better, branded product. The choice of medication resides with the patient, as does the cost!

Raising brand awareness with the end consumer

The patient is quite literally the "end consumer" when he or she swallows the medication. Patients are usually more familiar with the physical characteristics of the product (appearance, feel, taste, smell) than either the prescriber or the pharmacist. But do patients know what brands they are taking? The answer is often "NO". However, if pharmaceutical companies wish to build awareness and encourage loyalty for their brands, it is important that the patient is able to clearly identify their usual medication. "It's a little white tablet" does not give enough information to the doctor or pharmacist to identify to which product the patient is referring.

Elderly patients taking many medicines will often rely on the physical appearance of packaging and the product itself in order to remember which drug is which. This offers pharmaceutical companies an opportunity to differentiate their products through clever use of colour, shape, form, embossing and imprinting to ensure that their product is memorable.

Looking ahead

Pharmaceutical companies cannot promote their prescription drugs directly to "patient-consumers" (although there are plans in the European parliament to change this), they can offer support by providing valuable background information via disease-focussed websites, and by encouraging them to seek additional information from their doctors and pharmacists. Such initiatives can help improve patients' adherence to treatment and may also raise awareness of the treatment options within a particular disease area.

With the exception of major brands such as Viagra® or Xanax®, it is unlikely that drug names will soon be tripping off the patients' tongues when they collect their prescriptions from the pharmacy. However, thanks to 21st century communications, patients are certainly better informed about health issues and more demanding of their doctors and pharmacists to ensure that they receive the best possible treatment.

*Primary care is the term for the treatment that patients receive from their local medical practitioners

1. Potential savings from increased substitution of generic from originator medicines in Europe. Simoens et al . Journal of Generic Medicines, Vol 4, N°1, October 2006, pp. 43-45 (3)2006, pp. 43-45 (3)

• The Power of Patient Perception – Impact of galenic form

Can the form, shape and even the "feel" of a pharmaceutical product dictate the patient's perception of its efficacy and speed of action? Recent market research results suggest that they can.

Researchers interviewed one hundred patients receiving proton pump inhibitors for gastric reflux to identify their preferred dosage form and the reasons for their choice. The study, commissioned by Capsugel, was carried out by GfK Custom Research in September 2007. Patients were asked to describe differences between tablets and capsules of various shapes, sizes and colours.

The study showed how the dosage form can drive patient perception and product recall: essential information for pharmaceutical companies who need to differentiate their new brands in crowded markets. The threat of generic competition is ever present and will grow in the future – establishing a trusted brand is a major goal for healthcare companies.

Patient expectations and perceptions

Researchers asked the patients about their expectations regarding their treatment. The main requirement was rapid and lasting relief from pain and other symptoms. Patients also wanted drugs that worked quickly, were easy to take and did not have any side effects. A known brand and the quality of the product were also important parameters.

Colour, form and content are the aspects of their medication that patients remember most clearly. Although the traditional white tablet is still the best known and most established formulation, it is perceived as being less powerful than a capsule. Patients were particularly impressed by the liquid-filled capsule. They perceived it as offering rapid efficacy and good tolerability; the two key factors they were seeking in their medication.

Product differentiation – a marketing imperative

Four "P's" make up the marketing mix: Product, Price, Place (distribution) and Promotion. Product differentiation starts with physical appearance: colour, shape, and text on the shell of a capsule can all be used to create impact and make the product more memorable. The GFK study showed that printed capsules rate much more highly in comparison to other capsules or tablets in terms of product differentiation. If a company's focus is on establishing or maintaining a brand, an imprinted capsule should be the first choice.

Modern capsules are liquid-filled

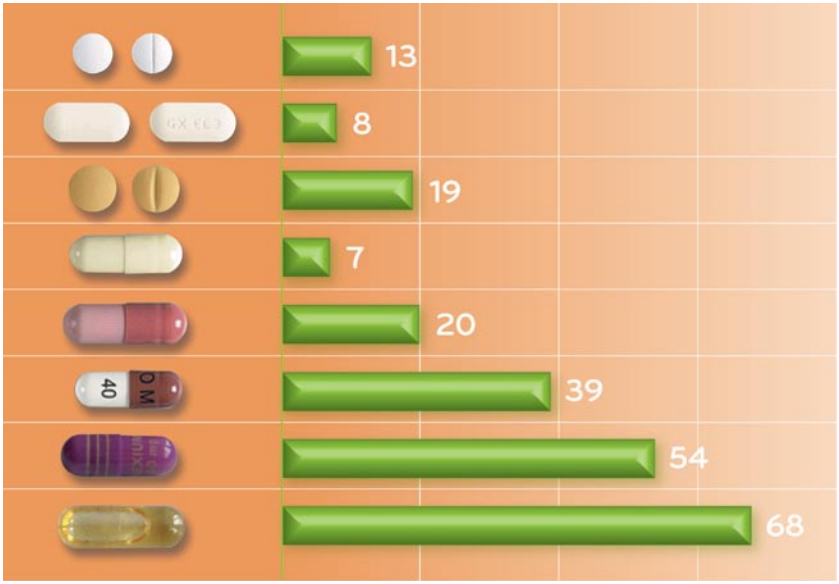
Even though traditional small white tablets are a familiar form and are generally "easy to take", patients prefer capsules, which they believe work better and faster than tablets.

Looking to the future, it is the attractive liquid-filled capsule that is likely to gain market share because it is perceived as being the best in terms of efficacy, tolerability and speed of onset. Patients like it because it is liquid-filled which looks efficient, dissolves quickly, is easy to take and looks as though it would be well tolerated. They describe the liquid-filled capsule as representing modernity and high quality.

Conclusions

Capsules offer an excellent opportunity for brand differentiation because of their versatility in terms of colour, contents and scope for printing. They can be designed to support the perception of desired product features and reinforce the patients' expectation of a positive treatment result. Imprinted capsules, particularly liquid-filled, will offer new opportunities for leading pharmaceutical brands of the future.

Top three tablets or capsules
that can be distinguished easily from the other forms.



Number of respondents =101

Respondents in %

Improving Compliance and Adherence through User-Friendly Packaging

Dr. David Spackman, Director Healthcare Packaging (Europe), MeadWestvaco Healthcare

Patients don't always take their medicine - why?

Poor treatment compliance results in poor outcomes. This can be disastrous for the patient and give a false impression of the drug's performance. Treatment outcome can be negatively affected by lack of patient compliance and it is six times more expensive to find a new patient than to keep an existing one. It therefore makes sense for the pharmaceutical industry to explore strategies that will encourage patients to take their medication and thus develop positive feelings about 'their' drug.

There are several reasons underlying non-compliance:

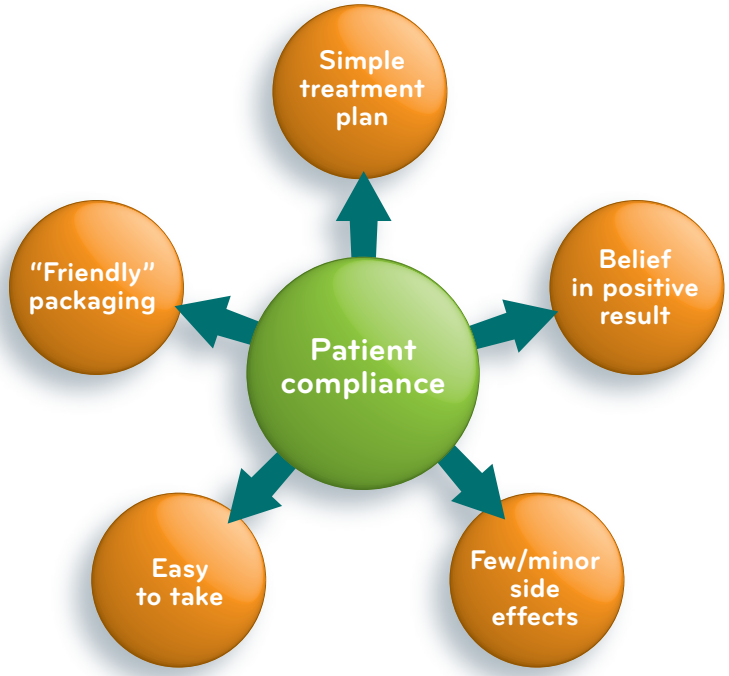
unintentional failure to follow instructions
- patient simply forgets to take their medicine
- he/she cannot afford to purchase the drugs prescribed or has difficulty in obtaining them from the pharmacy
- he/she cannot read or does not understand the patient leaflet because of the language or vocabulary used

lack of understanding
- patient does not understand or remember the doctor's instructions
- treatment plan is very complicated – multiple doses, difficulty in taking drugs at specific times (e.g. tid regimens) etc.
- patient does not understand why he/she needs the medication (may not have any symptoms)

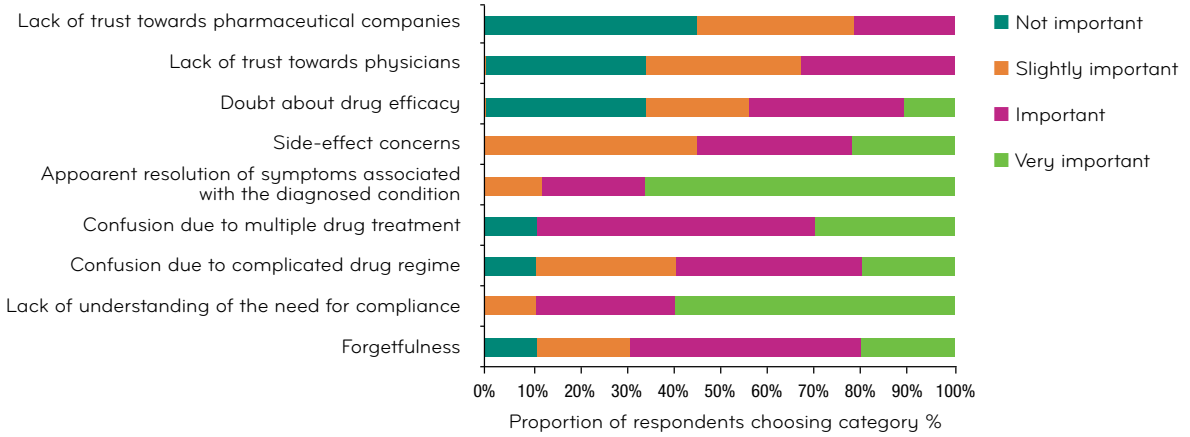
intentional non-compliance
- patient suffers side effects
- treatment is disruptive to lifestyle e.g. no alcohol allowed
- denial or embarrassment about the medical condition
- attitude that drugs are "bad for you" – mistrust of the doctors and the pharmaceutical industry

So what can be done to improve the situation and ensure that patients take medication correctly?

Compliance can be facilitated by using a simple treatment plan presented in a practical format. The patient is more likely to take his medicine if he understands why it is important and believes that it will bring positive results with few or minor side effects. Packaging that is easy to understand and easy to use even for elderly or confused patients is a key factor in encouraging patient adherence.



Perceived factors driving patient non-compliance



Source: Datamonitor's Patient Compliance Survey 2004

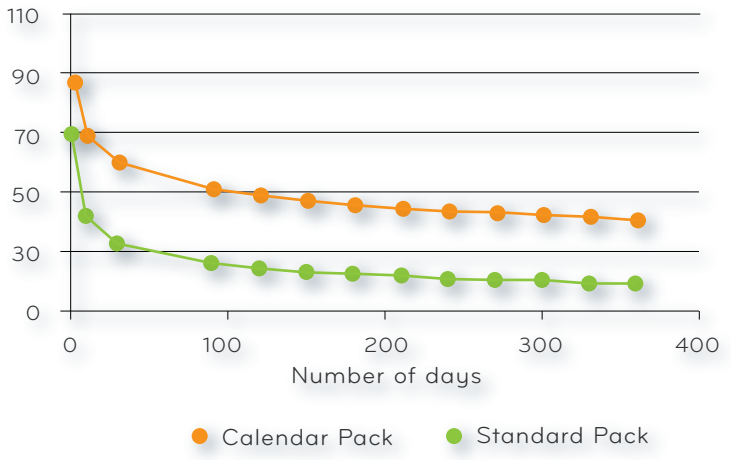
DATAMONITOR

Well designed packaging can:

- Promote compliance
- Emphasise important drug information
- Encourage patients to collect their next prescription
- Strengthen brand image and promote patient loyalty

All of these result in a better clinical outcome

Modelled adherence for Calendar Pack vs Standard Pack



Study conclusion : "Providing medications in a package that identifies the day each dose is intended to be taken and provides information on proper self-administration can improve treatment regimen adherence and treatment outcomes in elderly patients"[1].

Friendly packaging encourages adherence

Innovative packaging has been demonstrated to improve patient compliance and it is fast becoming an integral part of marketing strategy. Ready-to-dispense packs that contain unit doses for one treatment cycle and indicate on which days the doses should be taken, together with clear patient information, help to motivate and remind the patient to take the medication correctly. These are the basic requirements for a **compliance** package.

An increasingly elderly population has created a need for **senior-friendly** packaging, adapted for people who may have difficulty in manipulating packs and whose memories may not be as good as they were in the past.

Packaging should therefore be simple, easy to handle and straightforward to understand. This sounds like a simple recipe but often packaging design is dictated by cost and legal guidelines. Pharmaceutical companies do not necessarily view it as a valuable means of direct communication with the patient.

Checklist for compliance packaging

- Date & time – it should be clearly indicated on which date and at what time the dose should be taken. Time of day symbols could be used - ☽ ✹ ◔ ✹ ◘ ◘ ☼
- Blister packs with patient guidance e.g. capsules arranged in chronological with arrows showing the direction in which they should be used as for the contraceptive pill
- Information on WHY the drug should be taken – how it will affect the medical condition
- Information on HOW the drug should be taken – with food, before bedtime, avoid alcohol etc.
- Easy of opening – especially important for elderly people who have difficulties with manipulation: the patient should feel that he is in control of his treatment
- Large, clear print – essential for patients with sight problems

Proof that Compliance Packaging works

A recent study by Philip Schneider, Clinical Professor of Pharmacy at Ohio State University, looked at the impact of packaging on adherence and treatment outcomes in elderly patients suffering from hypertension1. In his study, 88 patients aged 65 years or older with high blood pressure, were randomised to receive their tablets either in daily dose blister packaging (Pill Calendar) or in traditional bottles of loose tables. The results clearly supported use of the compliance pack: patients using the pill calendar refilled their prescription more often on time (p=0.01), took their medication more regularly (p=0.04) and had significantly lower blood pressure over a 12 month period than the control group using bottles of tablets (p=0.01).

1. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. Schneider PJ, Murphy JE, Pedersen CA. J Am Pharma assoc (2003), 48(1): 58-63 2008.

Innovative packaging is a cost-effective way of improving patient compliance and supporting awareness not only for a brand but for entire product ranges. It helps to maximise product efficacy and encourages patient loyalty. Packaging can play a key role in lifecycle management.

• Innovation Strategies for Lifecycle Management – Keeping a competitive advantage

How do companies react when generic competition looms on the horizon?

All pharmaceutical companies with a successful prescription product have to plan for the day when the patent expires and they are faced with generic competition. The obvious response is to try to extend patent protection. Since the 1990s, patent protection within the European Union lasts for 20 years. Originator companies may extend this period by a further five years, through a Supplementary Protection Certificate. After this period, companies can seek to prolong protection by applying for further patents on the basis of new uses, indications, dosages and changes in formulation and presentation. Such strategies are disparagingly referred to by the generic houses as "evergreening".

Patents can be granted for:

- Basic composition, including new or alternative compounds
- Method of treatment – new use of known compound, different dosing, combination with other drugs
- Synthetic production
- Formulation and drug delivery
- Prodrugs that release active ingredient(s)
- Substances resulting from metabolism in body
- Different crystalline or hydrated structures
- Gene-markers showing response to drug therapy
- Devices, such as patches for drug administration

Which is the best strategy?

There is no "best strategy" for extending the life of a product. Each product has to be assessed individually according to its own characteristics and those of the market place. Common approaches are to develop new indications, to change the formulation or the delivery (e.g. once daily instead of twice). Whatever approach is preferred, product presentation can play an important role.

Based on its experience in drug formulation Capsugel has put together two hypothetical case studies on lifecycle management; the first product is prescription-only (Rx), and the second is available over the counter (OTC).

A "new improved" Rx product range

For this first case study, a hypothetical pharmaceutical company is faced with the challenge of maintaining maximum revenue from its blockbuster product, ColMex. ColMex is licensed for the treatment of peptic ulcers and gastroesophageal reflux. It is a global product that is well established internationally. The dose form is enteric coated pellets inside a Coni-Snap® gelatin capsule.

Two shades of green are used to distinguish the 10mg and 20mg dosage strengths. The capsule is overprinted with the

product name and dosage. The packaging is also clearly branded using the same product colours.

ColMex will reach the end of its patent life within the next year. Fortunately, the planning process is already well advanced as there are already two "new, improved" 2nd generation products ready to be launched.

The first of these products is ColMAX, a new formulation of the active ingredient that offers improved efficacy.

The other line extension is ColMAX Plus. It has the same new active ingredient as ColMAX combined with an antibiotic. This combination product is indicated for the eradication of the bacteria (Helicobacter pylori) that are associated with the development of peptic ulcers.

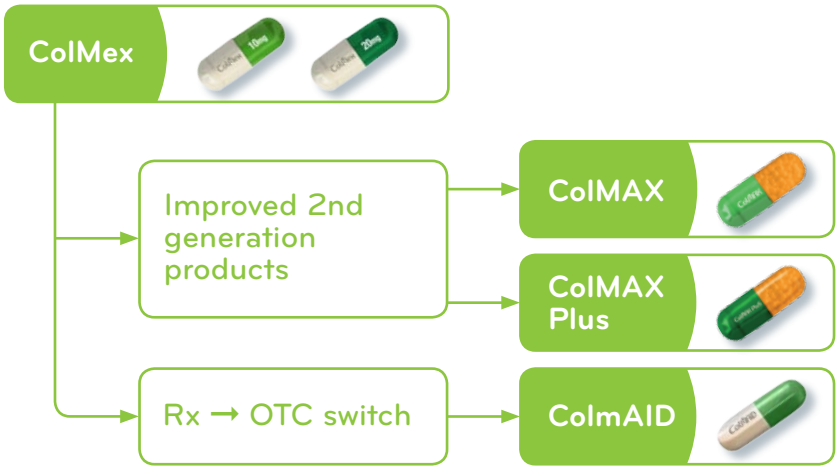
The presentation of these two new products is similar to original ColMex to help maintain brand recognition and patient loyalty. Differentiation is achieved by the use of different shades of colour for the capsule and packaging colours.

As ColMex nears the end of its patent, promotional effort will be switched to these superior second generation products thereby extending and prolonging the life of the brand. The same logo style and typefaces are used throughout the range to build on the established product image and reputation.

Taking Rx to OTC in gastroenterology

The company has also been exploring the potential of launching ColMex into the OTC market. A license has been obtained for the treatment of heartburn at a reduced dosage strength. Although the brand name has been changed, the style remains consistent with the prescription product: patient recognition enhances the perception of efficacy.

The new product - ColmAID - is clearly a close cousin of the prescription ColMex family but its arrival in the OTC market opens up a whole new target audience of pharmacists and consumers.



Stirring things up in a stagnant OTC market

So what happens in the OTC market where products may no longer have patent protection? BorNEX, from Codex Consumer Health (CCH), is the subject of our second virtual case study. It is a leading brand of the analgesic naproxen which also has anti-inflammatory and anti-pyretic properties. It is sold in pharmacies throughout the world and marketed directly to the consumer. BorNEX is formulated as a white coated tablet containing 250mg of naproxen. As it is not a patented molecule, differentiation of the CCH brand is essential to maintain consumer loyalty. Although sales of BorNEX are good, there is little opportunity for further growth as the pain market is saturated and sales are static.

CCH has worked on two life extension strategies based on consumer needs to maximise the commercial success of their product:

- Expanded indications – market segmentation through enhanced activity
- Line extension – 2nd generation by reformulation

Opportunities within the analgesic market

Three market segments have been identified as offering growth opportunities for BorNEX. These are migraine, menstrual pain and dental pain. To position BorNEX within these segments, it has to appeal to the patients suffering from each of these problems. In this case, the product has been tailored to each condition by the addition of specific vitamins: vitamin B complex to combat migraine, because of its role in mental stimulation; vitamin B6 for menstrual pain, to assist with red blood cell metabolism and to prevent anaemia; and vitamin D for dental pain, thanks to its role in the absorption of minerals required for tooth integrity.

Changing the dosage form from a tablet to a capsule means that combinations of different active substances are now possible. Capsules can be clearly branded by using product colours and printing with the brand name and logo. For BorNEX Dent, the Licaps, liquid-filled capsule has been selected because it allows the association of water soluble and insoluble active ingredients in the form of pellets in a liquid matrix.

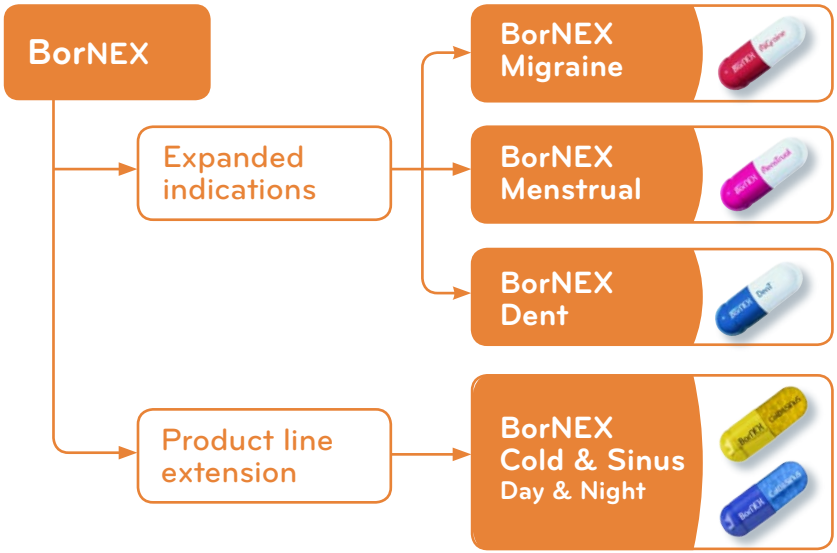
> According to a consumer preference study on OTC analgesia[1], capsules are associated with having no bad aftertaste and being easy to swallow. Liquid-filled capsules are associated with maintaining medication strength

		
BorNEX Migraine	**BorNEX Menstrual**	**BorNEX Dent**
Vitamin B Complex	Vitamin B6	Vitamin D
Red and White Coni-Snap® gelatin capsule	Pink and white Coni-Snap® gelatin capsule	Light blue and white Licaps® capsule

Opportunities in new indications

CCH identified a further opportunity for BorNEX within the market for treating cold and sinus problems. This new indication meant the existing product had to be combined with a new active ingredient: a nasal decongestant. It also had to be a rapid release formulation. BorNEX Cold & Sinus meets the different needs of the patient during the day and at night with two different forms: a yellow capsule for **Day** with the addition of vitamin C to combat febrile state; and a blue capsule for **Night** with the addition of an antihistamine, diphenhydramine, to stop a runny nose and to aid sleep.

Rationale for choice of dosage form : Coni-Snap® gelatin capsule allows the combination of active ingredients in rapid release pellets



By adopting the two lifecycle management strategies described here, the company has successfully expanded its brand share within the existing analgesic market and also extended further afield into another profitable market.

Must "All good things come to an end"?

The secret behind maximising the lifecycle of a product is to plan ahead and be innovative. A successful product can become a product range by building on the success of the original brand. Products can be given a new lease of life through new formulations and drug delivery forms, and rejuvenated by new dose forms and a strong brand image.

1. Consumer preference study on solid dosage form (Capsugel 2003). Available from the Capsugel Library at www.capsugel.com

• Pharmaceutical Form – Who decides?

Expert View, Dr Matthias Müller, Clinical Research Director, Sanofi Aventis Research and Development

Dr Matthias Müller is responsible for Phase II and III clinical development programmes across a broad range of therapeutic indications – internal medicine, nephrology, and pain - in the International Clinical Development department at Sanofi Aventis. He also oversees Phase I trials and works closely with the preclinical teams. We were interested to know when decisions on pharmaceutical formulations and the dosage form are made during the development of a pharmaceutical product and how such decisions are made. In this interview Dr Müller describes the process and suggests ways that it could be improved, as well as showing how the form of a drug can play a key role in lifecycle management.

What aspects should be considered when deciding on the best formulation for a new compound?

The starting point for any galenic decision is to consider the physicochemical characteristics of the drug candidate; its hydrophilicity or lipophilicity, solubility, crystallisation properties etc. For example a strongly hydrophilic compound cannot be used for a transdermal patch as only lipophilic compounds can move through the dermis.

The target indication and intended marketing positioning drive drug delivery choices such as frequency of dosing, need for dose escalation, rapidity of onset and whether controlled release is necessary.

The preferred route of administration is dictated by the indication: it can be oral as liquid, tablet or capsule; i.v. injection; subdermal implant; transdermal patch; nebuliser; or another novel dosage form.

During the clinical development process when are formulation decisions made?

In Phase I studies in healthy volunteers, the objective is to confirm the initial findings from pre-clinical in vitro and in vivo studies and to define the desired product profile in humans. At this early stage relatively little consideration is given to the final dosage form of the drug and preliminary galenic service formulations are used. Administration to the volunteers is usually oral or by i.v. injection. The compound may require manual preparation for these studies e.g. an oral drinking solution with limited stability, and the final dosage can still be uncertain. The galenic formulation development process continues in parallel with Phase I. Data on the pharmacokinetic and pharmacodynamic properties, drug interaction and tolerability collected during this phase enable the formulation to be refined before moving to Phase II studies.

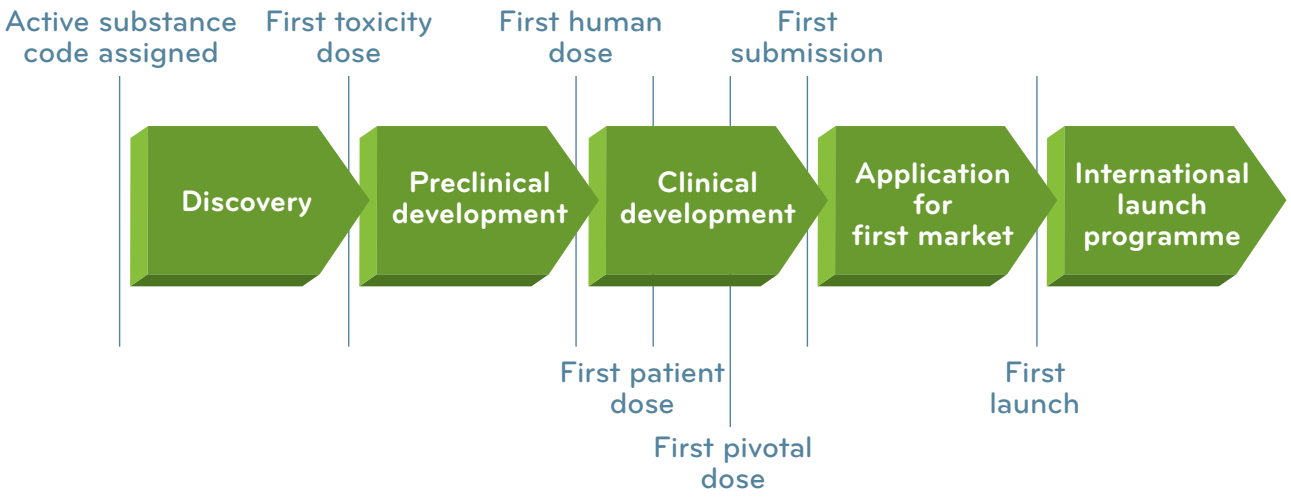
For Phase II studies, the drug formulation should already be close its final marketed form. For example, if a prolonged release capsule is chosen, ideally the studies should use this capsule. However, often this is not possible because of a backlog within the galenic development process. If any significant formulation changes are made before launch, it is necessary to carry out new bioequivalence studies which are both costly and time consuming so this is the main decision point on pharmaceutical form in the development process. The project team bases its decision on the pre-clinical and Phase I study results, the recommendations of the galenic specialists and marketing requirements.

In some Research and Development (R&D) led companies there may not be sufficient marketing input at the start of Phase II. This can cause problems in the future if the formulation does not meet the needs of the market.

Fortunately, although Sanofi Aventis has a strong R&D lead, the management ensures that there is marketing involvement from Phase I when the desired product profile, based on future market positioning, is developed by the first core project team which is made up of the project leader and representatives from preclinical and clinical development, and from marketing.

By the time the drug enters Phase III, the final dosage and

Key R&D milestones and intervals



pharmaceutical form have been defined. As Phase III studies are comparative it may be necessary to over capsulate the new drug and its comparators for blinding purposes. Care is taken that no components are changed to avoid any need to retest bioavailability. Coloured capsules or tablets may be used in Phase III, but overprinting with branding figures and logos is not used before launch.

Who makes up the project team and what is its role?

Before a new compound goes in Phase II clinical development, an expanded project team is formed. This is directed by the project leader, who has already been involved since the pre-clinical stage. He or she usually has a broad background across different areas involved in product development. Such experience is essential as he/she is responsible for preparing the business case for the new drug. The business case must be validated by management before budget can be allocated and the project can proceed.

The project leader may be assisted by a project manager whose main responsibility is to ensure that timelines and budget are respected. Other members are from preclinical and clinical development,

regulatory affairs, chemistry, manufacturing and quality control, and marketing.

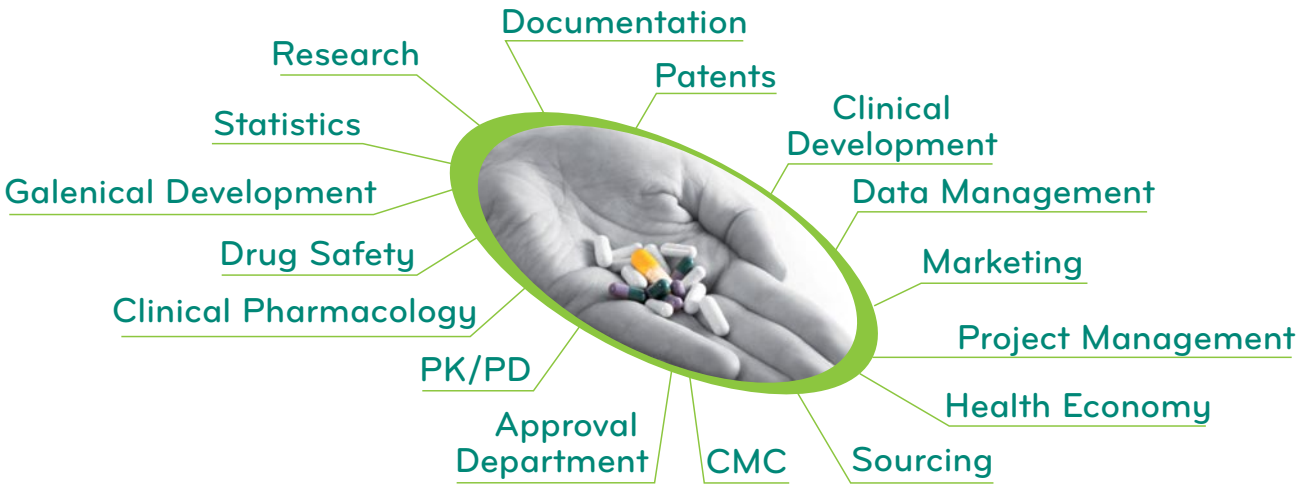
The project team should be empowered to carry the project forward through clinical development and into the launch phase. In an "ideal world" it should be the project team that prepares the case for all of the important decisions to be taken or actioned by management. Management can however, over-rule a proposal or decision taken by the team for financial, portfolio or other strategic reasons. Potentially such interference can lead to a readjustment of the overall project timelines or objectives.

How does marketing strategy influence formulation?

Generally speaking there are two sorts of companies: those that have an R&D focus and those that have a commercial focus. In R&D companies, marketing tends to become involved later on in the development process whilst in more commercially oriented companies, there is early involvement, even before the compound reaches clinical development.

Ideally marketing should be influencing formulation decisions as soon as the compound has been identified as a development candidate and is about to enter the clinical development phase. The desired target drug profile is developed with marketing to guide future development plans. It usually takes between fifteen and eighteen months for a drug candidate to complete the preclinical phase and move to its first administration in man.

In parallel to the clinical development programme, marketing must define future marketing requirements by studying market data, analysing competitive intelligence and talking to external experts. The results of this in-depth market



"Capsules are simpler to produce than tablets. You just need a stable powder that can be encapsulated"

assessment influence the strategy of the overall development programme for the drug as well as the future international marketing strategy.

The most common administration route is oral. How do companies decide whether to choose a tablet or a capsule?

Companies are keen to get to their products to market as rapidly as possible in order to maximise return on investment. The average cost of developing a new drug is 800 million euros and it can take eight to twelve years to get to market. There may be additional pressure to accelerate launch to when the product is potentially first-in-class thereby conferring a marketing advantage.

For many oral formulations, the simplest form is a capsule filled with a stable, quick release powder. Although many companies still develop tablets for initial launch, tablets can often be more complicated to manufacture with more production steps involved, and they require more excipients than capsules. In some cases, often dependent on the complexity of the mixing and tablet coating processes, the overall total cost difference between tablets and capsules is not significant.

How can dosage form impact on the lifecycle management of a product?

Early in the planning process it is important to consider future line extensions so that new formulations, such as sustained release for once daily dosing, can be introduced a relatively short time after the initial launch. A new formulation and presentation serves to create interest and product awareness within the market place and results in further sales and profitability for the company.

As the product nears the end of its patent life, a novel formulation can mean a patent extension which protects the brand from generic products.

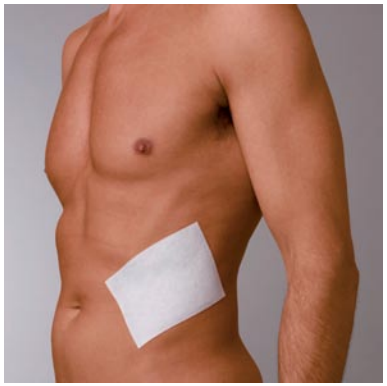
New formulations can be achieved by for example by:

- changing pharmacokinetic properties of the compound
- modifying the chemical structure but focussing on the same target

These future possibilities are

identified during the initial clinical development process and decisions to develop them should ideally be made before the first product is launched.

Some drugs keep the same formulation but take on a new pharmaceutical form for which they are granted a further patent or at least document protection. For example, a synthetic opioid, buprenorphine; has been available since the 1980's for intravenous or sublingual application. In 2001, a buprenorphine transdermal matrix patch was launched and obtained a patent for this new galenic form. Initially the patch was launched for three days treatment then subsequently new patches lasting for a longer application period have been introduced as line extensions.



The key is to bring together all the main players... from an early stage in the development of a new drug

How do you believe that choice of pharmaceutical form could be improved in the future?

The decision process needs to be based on open cross-functional discussions throughout the development process. No single department should be responsible for making decisions. The key is to bring together all the main players – technical, regulatory, clinical development, marketing - from an early stage in the development of a new drug and ensure that they have ownership of the project and can make important decisions based on the available scientific, clinical and marketing data focussing on the main objective of achieving market access for the new drug in its specific indication and galenic formulation.

Recent article abstracts

Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration

Ewart T. Cole, Dominique Cadé, Hassan Benameur

The encapsulation of liquids and semi-solids provides solutions for convenient delivery through improved oral absorption of poorly water-soluble drugs. In addition, low dose (content uniformity), highly potent (containment), low melting point drugs, those with a critical stability profile and those for which a delayed release is required are candidates for liquid or semi-solid formulations. Both hard and soft capsules can be considered and in each case the capsule wall may comprise gelatin or some other suitable polymer such as hypromellose. The choice of a hard or soft capsule will depend primarily on the components of the formulation which provides the best absorption characteristics as well as on the physical characteristics, such as the viscosity of the formulation and the temperature at which the product needs to be filled. Numerous excipients are available for formulation of lipid-based systems and their compatibilities with hard gelatin capsules have been tested. The availability of new enhanced manufacturing equipment has brought new opportunities for liquid-filled hard capsules. Filling and sealing technologies for hard capsules, provides the formulator with the flexibility of developing formulations in-house from small scale, as required for Phase I studies, up to production.

Effect of excipients on breast cancer resistance protein substrate uptake activity

Benameur H.
Tetsuo Yamagata, Hiroyuki Kusuhara, Mariko Morishita, Kozo Takayama, Hassan Benameur, Yuichi Sugiyama

Abstract

Breast cancer resistance protein (BCRP/ABCG2) plays an important role in drug disposition. To examine whether some currently used excipients could inhibit its function, we measured the uptake of [3H]mitoxantrone in BCRP-, P-glycoprotein (P-gp)- or green fluorescent protein (GFP)-expressing cells, in the presence or absence of 15 kinds of currently used excipients. Of 15 excipients, five (Cremophor EL, Tween 20, Span 20, Pluronic P85 and Brij 30) increased the uptake of [3H]mitoxantrone in BCRP-expressing cells. On the other hand, ten (Cremophor EL, Cremophor RH40, Tween 20, Tween 80, Span 20, Pluronic P85, vitamin E TPGS, Brij 30, Myrj 52 and Gelucire 44/14) significantly increased uptake in P-gp-expressing cells. No significant effects on intracellular ATP levels were observed following treatments with the excipients that inhibited BCRP function. Taken together, this study demonstrated that some excipients might be potent BCRP inhibitors, and there may be differences in the effects of excipients on the functions of BCRP and P-gp.

Improvement of the Oral Drug Absorption of Topotecan through the Inhibition of Intestinal Xenobiotic Efflux Transporter, Breast Cancer Resistance Protein, by Excipients

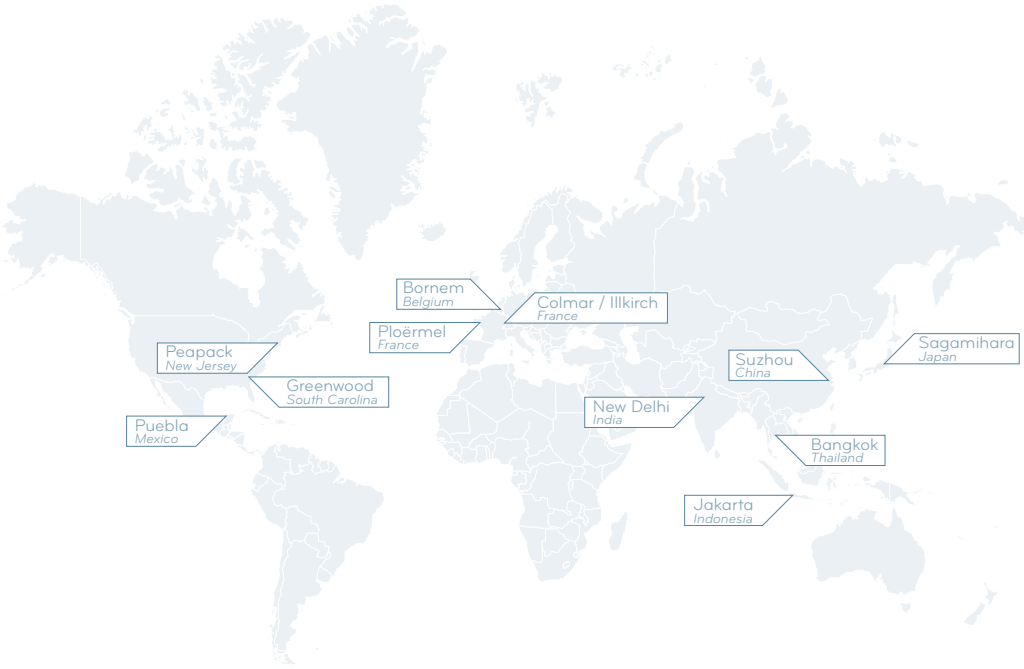
Tetsuo Yamagata, Hiroyuki Kusuhara, Mariko Morishita, Kozo Takayama, Hassan Benameur, and Yuichi Sugiyama

Recently, breast cancer resistance protein (BCRP/ABCG2) has been shown to limit the oral absorption of its substrates in the intestine. The purpose of this study was to examine whether excipients can be used as inhibitors of BCRP, to improve the oral drug absorption of BCRP substrates. In wild-type mice, Pluronic P85 and Tween 20, given orally 15 min before topotecan administration, increased the area under the plasma concentration-time curve (AUC) of topotecan after oral administration (2.0- and 1.8- fold, respectively). In contrast, Pluronic P85 and Tween 20 were less effective (no significant difference) on the AUC of topotecan after oral administration in Bcrp (_/_) mice (1.2- and 1.2-fold, respectively). Pluronic P85 and Tween 20 given orally did not affect significantly the AUC of topotecan after intravenous administration in wild-type and Bcrp (_/_) mice. Moreover, we determined the mucosal-to-serosal absorptive transport of topotecan using everted mouse ileum. Pluronic P85 and Tween 20 significantly increased the intestinal absorption rate of topotecan in everted sacs from wild-type mice whereas, in everted sacs from Bcrp (_/_) mice, the absorption rate was 2.1-fold greater than that in wild-type mice, and these excipients were not significantly effective. There was no significant difference in the intestinal P-glycoprotein (P-gp) expression and serosal-to-mucosal secretory transport of rhodamine 123, a typical P-gp substrate. Taken together, these results suggest that Pluronic P85 and Tween 20 can improve the oral bioavailability of BCRP substrates by inhibiting BCRP function in the small intestine.

Evaluation of the Impact of Surfactant Digestion on the Bioavailability of Danazol after Oral Administration of Lipidic Self-Emulsifying Formulations to Dogs

Jean F. Cuine, Claire I. Mcevoy, William N. Charman, Colin W. Pouton, Glenn A. Edwards, Hassan Benameur, Christopher J.H. Porter

Lipid-based formulations of danazol with varying quantities of included surfactant have been examined in vitro and in vivo. Formulations comprising fatty acid ester surfactants were readily hydrolysed during in vitro digestion, although Cremophor RH40 (CrRH) was less effectively hydrolysed than Cremophor EL (CrEL). Formulations comprising high quantities of digestible surfactant also appeared to less effectively prevent danazol precipitation during in vitro evaluation. These trends were replicated in vivo where danazol bioavailability in beagle dogs was higher after oral administration of self-emulsifying formulations employing 55% (w/w) CrRH when compared with CrEL. The oral bioavailability of danazol after administration of drug formulated in surfactant alone, however, was poor. Studies using predispersed and encapsulated formulations of CrRH subsequently suggested that the low bioavailability of the single surfactant formulations reflected poor dispersion. Mixtures of surfactants, improved dispersion and good oral bioavailability of danazol was evident after administration of formulations comprising CrRH and either Pluronic L121 or Gelucire 44-14, in spite of evidence of danazol precipitation during in vitro digestion of the Gelucire formulation. These data suggest that effective dispersion and resistance to precipitation during both dispersion and digestion are key design parameters for lipid-based formulations comprising high proportions of surfactant.



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