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# How to develop and register pharmaceutical products faster

advice from an international  
excipient supplier

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# How to develop and register pharmaceutical products faster – advice from an international excipient supplier

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Based on a presentation made during the AFI's 39<sup>th</sup> Symposium, Montecatini Terme, March 27, 1999

The key issues which the pharmaceutical industry is facing today concern ever-increasing development costs, and the changing regulatory environment, set in a context of fierce competition. The result is that globalization, time to market, innovative and patented technologies and product differentiation have become crucial factors in successful product development and launch.

## Raw material supply in industry

A pharmaceutical product is made up of the active substance and one or more excipients. Excipients facilitate processing on high-speed machines and add certain characteristics to the product; these characteristics are specific to the type of excipient used. Excipients and their particular functionalities usually contribute to the overall product quality. Specific functionality that helps to optimize the final pharmaceutical product can be manufactured into the excipient with the know-how of the excipient manufacturer.

For these reasons, the pharmaceutical industry needs to choose a supplier offering a wide range of excipients, each providing different advantages, in order to select the most appropriate type for development and efficient manufacture.

For example, from the wide range of empty two-piece capsules which Capsugel produces (*Table 1*), the customer can choose capsules suited to pre-clinical animal studies, or to clinical trials, or to the market place. All are geared to facilitating development and production – the Licaps®, for instance, is a hard gelatin capsule with a unique design that prevents leakage of a liquid formulation within a hard gelatin capsule.

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### Pharmaceutical industry

- |             |                   |
|-------------|-------------------|
| • PCcaps®   | • Coni Snap Supro |
| • DBcaps®   | • Licaps®         |
| • Snap Fit  | • Press-Fit™      |
| • Coni Snap |                   |

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*Table 1: Capsugel's two-piece hard gelatin capsule product range*

## Towards globalization

Within the European Union (EU), a product that is intended to be introduced in more than one EU country must go through the European Medical Evaluation Agency (EMA), either by the centralized procedure or the Mutual Recognition Procedure (MRP), where the product is evaluated by one or two Reference Member States (RMS).

In the light of the substantial costs which pharmaceutical development now represents, the major advantage of EU-wide approval is that the individual company obtains access to all European member state markets, providing the opportunity to fully exploit the product's potential, either by selling it directly itself, or by licensing-out the sales activity to another company.

Additionally, the on-going International Conference on Harmonization (ICH), aimed at bringing about common requirements for pharmaceutical product authorization in Europe, USA and Japan, will one day mean that a single product dossier will be acceptable world wide, and opens up the prospect of launching from the outset on a global scale.

From this it follows that if a product is to be successfully produced and marketed on a global scale, companies will need excipient suppliers which themselves have a global presence and which provide the same product quality everywhere in the world.

#### Pharmaceutical industry

- Greenwood, USA
- Bornem, Belgium
- Colmar, France
- Sagami, Japan
- Puebla, Mexico
- Rio de Janeiro, Brazil
- Bangkok, Thailand
- Cibinong, Indonesia
- Suzhou, China

Table 2: Capsugel production plants around the world.

With nine plants world wide (Table 2), all working to the same standards of quality and production, Capsugel adheres to every requirement necessary to ensure that quality is identical wherever a product is supplied. And its unique added-value support services – such as the Expert System, the Multistate File, the List of Colorants and the Biopharmaceutics Drug Classification – mean that the company is recognized the world over by regulatory authorities and pharmaceutical industry alike, as a reliable partner in high-quality pharmaceutical development.

#### Speed-up development with an excipient supplier

Gaining the competitive edge is no longer an issue that can be left until the product is commercialized. Within every strategic therapeutic area, companies are investigating new pharmacological interventions in the hope that this will lead to a new class of compounds.

Order of entry	Market share (%)
1	38
2	18
3	13
4	6
5	4
6	2

Table 3: Market share by order of entry

But as soon as a new class of drugs appears, it takes no time at all for several other companies to have comparable products under development. Subsequent market share and commercial success then become a matter of the time required to develop and launch these products. Table 3 shows the market share that can be expected according to order of entry.

To be first on the market requires an efficient pharmaceutical development program, which is largely dependent on the early availability of a robust formulation. The formulation should therefore be simple, to achieve the desired release profile, easy to scale-up to production level, and able to pass from Phase I right through to market introduction without needing significant modification.

In general, formulation utilizing hard gelatin capsules requires only a very limited number of well-established excipients that can be mixed and filled directly into the capsules by a well-known process (Table 4), so helping to avoid unexpected surprises in the course of pharmaceutical development.

Hard gelatin capsules:

- need less active ingredient
- require simple mixing/filling, are easy to scale-up
- facilitate formulation
- create continuity from Phase I to market
- provide flexibility in development and production

Table 4: Efficiency in pharmaceutical development with hard gelatin capsules

Constantly on the lookout for ways of supporting the pharmaceutical industry, Capsugel has now addressed the need for rapid formulation development with a unique software tool, the **Expert System**, which was jointly developed by universities in Europe, Japan and the USA (Table 5) and by pharmaceutical companies all over the world (Table 6). The system processes a pharmaceutical product's main characteristics, to provide suggestions at preformulation stage based on scientific and industrial expertise.

#### University experts

- Prof. M. Newton, University of London (Europe)
- Prof. L. Augsburger, University of Maryland (USA)
- Prof. M. Hashida, University of Kyoto (Japan)

Table 5: University experts involved in the Expert System

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### Pharmaceutical industry

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- Abbott
  - AHP
  - BMS
  - Daiichi
  - Eisai
  - Fujisawa
  - Hoffmann-La Roche
  - Glaxo Wellcome
  - Kanebo
  - HMR
  - McNeil
  - Merck & Co.
  - Parke-Davis
  - Pfizer
  - RPR
  - RW Johnson
  - Sandoz
  - Sankyo
  - Tanabe
  - Schering-Plough
  - SmithKline Beecham
  - Synthélabo
  - Takeda
  - Schein
  - Yamanouchi
- 

*Table 6: Industrial experts involved in the Expert System*

There is no doubt that the Expert System, with its capacity for substantially reducing the time involved in formulation development, is of increasing interest to the pharmaceutical industry. And, because hard gelatin capsules as a dosage form require less active to arrive at an appropriate formulation, we can expect them – together with the Expert System – to play an increasingly dominant role in pharmaceutical development.

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- rapid formulation suggestions based on the major product characteristics
  - interaction with the Expert System to fulfil company requirements
  - provides all information on the formulation created including the Pharmaceutical Development Report
  - created formulations stored in a history file
  - provides learning system by regularly incorporating updated feedback
  - proven to be highly efficient
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*Table 7: Features of the Expert System which facilitate formulation*

The goal the experts set for themselves in setting-up the system is to ensure a robust formulation for a product through providing practical information specifically geared to the most important needs of very early-phase development. In addition, the Expert System takes into account varying company policies and the global acceptance of the formulation, as well as drug stability and production-scale filling.

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- pharmaceutical technical specification and procedures
  - information on product specification and quality
  - important information on capsule filling, packaging and storage
  - recognized by regulatory experts for dossier preparation in Europe
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*Table 8: Features of the Multistate File*

In the course of its development, several improvements were incorporated, such as the provision of the Pharmaceutical Development Report and an Optimization Package to fine-tune the formulation as necessary. It is kept up to date as a learning system by regular feedback on formulations developed through its use, and by regular meetings with the experts who devised it. The major features of the Expert System are listed in *Table 7*.

Regulatory considerations are another important aspect of time to market. Preparing the dossier for submission to the authorities is critical. And here there is a definite advantage in utilizing a supplier which is itself a global player and which can provide the appropriate quality standards and documentation for the varying application requirements and formats across the different regions.

A further help in product information for preparation of the dossier comes with Capsugel's **Multistate File**, which contains all the technical procedures applied to the quality control of its hard gelatin capsules, as well as their specifications (*Table 8*). It can also be used to confirm that the correct analytical procedures for pharmaceutical products are in place and in accordance with the set specification, whether that of the EU, USA or Japan, and the information can then be transferred directly to the pharmaceutical dossier.

### Regulatory guidance

Time to market is also related to continuity of the dosage form from Phase I through to launch, since every modification requires proof of equivalence – and, especially, of bioequivalence – with the earlier product formulation or dosage form.

Due to its straightforward formulation and production, its flexibility in terms of batch sizes (*Table 4*), and the predictability of drug release which it offers, the hard gelatin capsule is usually the first dosage form used in pharmaceutical

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development. Remaining with this formulation throughout, rather than changing, will avoid the expensive and time-consuming additional studies needed to prove product equivalence, as well as any unexpected performance differences that might otherwise be encountered.

However, modification of the formulation or production process is often required during development and scale-up of a new product. And sometimes a switch to a different dosage form is one of the targets of the development program, in which case it will need to be performed in an appropriate way.

Unfortunately, there are still no clear guidelines that define the investigations necessary to prove the equivalence of the new version as compared with the original product. So, to avoid any surprises during the registration process that could retard the marketing authorization, companies generally perform substantial *in-vivo* comparison studies, whether or not these are actually necessary.

From a scientific point of view it is accepted that solubility and permeability are the critical product characteristics that can be significantly influenced by the formulation. With the **Biopharmaceutics Classification System (BCS)**, drugs are categorized according to their solubility and permeability into four classes, each influenced by the formulation to varying degrees. The BCS provides guidance on *in-vitro* and *in-vivo* tests to be performed to prove the safety of the new version. For example, if a product is highly soluble and permeable (class I) the *in-vitro* dissolution data demonstrating equivalence between both products can be regarded as sufficient.

To establish the BCS in pharmaceutical regulation, Capsugel organized symposia in Princeton (USA), Geneva (Switzerland) and Kyoto (Japan), involving experts from the industry as well as from the regulatory authorities. One of the outcomes of this series of symposia was the inclusion of the BCS in US Food and Drug Administration regulations. The symposia findings have since been published

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- to classify drugs according to their solubility/permeability
  - to provide guidance in terms of product variations, line extensions or generics
  - to facilitate regulatory clearance
  - to avoid excessive bio-studies
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Table 9: Objectives of the Biopharmaceutics Classification System (BCS)

and are held in the Capsugel Library (Document BAS 190). The major objectives of the BCS are summarized in Table 9.

The therapeutic efficacy of a drug is not only dependent on its potency at the site of action but also on its absorption, distribution and pharmacological characteristics in the body. By understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug substance, the appropriate formulation targets for time and rate of drug delivery for an optimized product can be defined and developed.

From the data gathered in pre-clinical and early clinical development the PK and PD data can be linked for **PK/PD modeling**, which allows predictions to be made of the likely clinical performance of an investigational new drug. Since Phase II and III clinical trials generally represent the most time-consuming part of drug development, the use of PK/PD modeling is important, as it secures the design of an effective, straightforward clinical trial program that, together with the optimized formulation, substantially helps to minimize development time.

To establish guidance and agreement on PK/PD modeling in development and registration, Capsugel organized a symposium on PK/PD modeling in Tokyo (Japan) which included world experts from the industry and regulatory agencies, and plans to continue these symposia in the USA and Europe. The conclusions of the symposia on PK/PD modeling and the BCS have been published and are held in the Capsugel Library.

Capsugel's network of experts can also provide practical support in speeding-up development and product registration that goes far beyond the supply of empty gelatin shells.

### The technical help available

Clinical trials are performed to a very tight schedule to hasten the development of a new product and, depending on the results, additional trials may also have to be performed at very short notice. In

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- unique shape to fill solid oral dosage forms of between 9 and 17 mm
  - colors acceptable world wide
  - immediate delivery
  - 3 sizes and 3 colors available
  - cannot be re-opened without damage
  - fillable on normal capsule-filling machines
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Table 10: Features of DBCaps®

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particular, in double-blind trials comparing the efficacy of a new product against an existing one, product-blinding as required by Good Clinical Practice (GCP) can be very difficult. It was to help fulfil the requirements for easy and rapid blinding for double-blind clinical trials that Capsugel developed the DBcaps® (*Table 10*).

The shape of this capsule is suitable for filling solid oral dosage forms of up to 9 mm in diameter and 17 mm in length, on normal capsule-filling machines, and it prevents the capsule being re-opened without damage. The colorants used make the capsule shell completely opaque and are accepted world wide. Through a dedicated logistics program DBcaps® can be delivered immediately.

### Product differentiation

Colored or imprinted dosage forms are often used, as a means of differentiating a product from the competition, to create a global brand image or to improve product identification and patient compliance. Capsugel's **List of Colorants** – used as a reference book by regulatory authorities – offers a quick way of identifying the colors and their constituents that are acceptable on a global basis, since it summarizes the status of 35 colorants in 80 countries (*Table 11*). It is based on studies establishing the functionality of colors, as well as their correct combination, which Capsugel carried out in close collaboration with experts.

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- acceptability of colorants for pharmaceutical products
  - includes 35 colorants covering 80 countries
  - provides information on functionality of colors
  - provides guidance on the right color combination
  - is used by regulatory authorities as a reference book dossier preparation in Europe
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*Table 11: Features of the List of Colorants*

To make the List of Colorants even more practical for pharmaceutical development and to address the needs of company marketing and purchasing departments, the original publication has since been brought out as a CD-Rom. The CD-Rom allows the easy creation of global color combinations and displays them immediately in 3-D form. Information on the functionality of each color combination and their differentiation by elderly can be accessed directly. An order form for samples of the selected color combinations is included and can be faxed or e-mailed to Capsugel for fast delivery.

As with all documents mentioned in this paper, the List of Colorants is available through the **Capsugel Library**, which provides scientific literature on all aspects of hard gelatin capsules as a dosage form.

### Product improvement

The most important key to successful long-term evolution is a company's capacity for continual innovation. And the innovative strength of a company needs to be supported by new developments from excipient suppliers. Not surprisingly, Capsugel has a strong R&D center that constantly brings new products and technologies to the market, often as a direct response to customer needs.

For example, there have been requests from companies with products nearing the end of their patent protection for appropriate line-extension developments, especially if switching to over-the counter product versions. Here, dividable dosage forms, or higher dosages in smaller capsules, combined with the right color combination to improve patient compliance, can be very powerful marketing advantages.

Such needs have been addressed with Capsugel's development of its patented **Press-Fit™ technology**, where an oval-shaped caplet is coated with a prefabricated capsule shell by a shrinking process. The ease of use, and the simplicity of setting-up the Press-Fit™ technology in-house, offers a potential benefit to pharmaceutical companies' product life-cycle management programs.

With today's high-throughput screening methods, the compounds selected tend to be highly lipophilic. As a result, poor solubility and permeability are among the major challenges in the formulation development of a new product. Out of the different technologies investigated to overcome this issue, lipid-based formulation has been identified as one of the most powerful for improving bioavailability.

The hard gelatin capsule is a highly suitable container for developing a solid oral dosage form from liquid or semi-solid lipid formulations. **Licaps®** is a newly developed capsule that provides an effective tight fit even for liquid formulations. However, its mechanical closure system is not always adequate for the low-viscosity products on the market. Consequently, the next step requested by the industry was a simple and effective sealing process.

With its long experience in mechanical engineering, Capsugel has developed a dedicated machine

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that seals the capsules, to US Pharmacopeia standards, by hydroalcoholic fusion. The basic operations of the **LEMS** machine (**L**iquid **E**ncapsulation **M**icro**S**pray) involve spraying about 50 µl of a hydroalcoholic solution directly between the cap and body of the already filled and closed capsule, followed by an evaporation process. Both spraying and evaporation are performed in less than one minute, providing a machine throughput of 30,000 capsules an hour.

With the patented **Licaps®/LEMS technology** pharmaceutical companies now have the unique opportunity to develop and produce lipid-based formulations in-house, while retaining full proprietary rights and control over the commercial exploitation of their new products.

Apart from the Licaps®/LEMS technology itself, Capsugel provides substantial further support for formulation development, scale-up and production. Working with leading university and pharmaceutical industry experts, it has produced state-of-the-art guidelines on lipid-based formulation development, which will be regularly updated and improved.

Scientific exchange on the specific characteristics of a drug, as well as on the development strategy set for the product by the company, can be extremely valuable for formulation scientists. With its network of experts Capsugel is able to provide personal scientific exchange and consultancy with leading experts in this domain, on terms of strict confidentiality.

Once a company has selected suitable formulations for Licaps®/LEMS technology, the next issue to be addressed concerns compatibility of the formulation with the gelatin shell properties on the high-speed filling and sealing machine. Capsugel is happy to share its capsule expertise in these technical areas by running compatibility studies with customers' formulations as well as feasibility studies for filling and sealing.

When the product enters the clinical phase, clinical samples must be produced. To provide the pharmaceutical industry with easy access to these new technologies, Capsugel has established **alliances** with Quintiles in Europe and Eurand in the USA where the Licaps®/LEMS and the Press-Fit™ technology are installed in a Good Manufacturing Practice (GMP) environment for clinical trial batch production or contract manufacturing.

To better fulfil the future needs of the pharmaceutical industry, Capsugel recently acquired a soft gelatin capsule production unit, as a start toward realizing its vision of creating a **technology platform** different from what is available today.

## Summary

To develop high quality and modern pharmaceutical products companies need excipient suppliers that offer a full product range and services such as Capsugel's capsule portfolio, which includes capsules for pre-clinical, clinical and marketing purposes.

In addition to all this, the hard gelatin capsule as a dosage form itself facilitates and speeds-up development, through the flexibility and ease of formulation which it offers – along with the prospect of seamless continuity from Phase I through to the market place.

Companies looking towards globalization require partners offering a global presence and acceptance by the regulatory authorities as well. With nine plants all over the world Capsugel can supply its hard gelatin capsules to the same regulatory standards of quality and production, wherever its customers are based.

It's open to excipient suppliers to identify the requirements of the pharmaceutical industry, simply by listening to it carefully. And – since each supplier has in-depth experience and knowledge of his own area – he is in a good position to support the industry as well as the regulatory authorities in facilitating and speeding-up the market authorization of pharmaceutical products.

Capsugel has already moved in this direction, by creating a number of tools which are recognized by the pharmaceutical industry and the regulatory authorities. There is the Expert System for formulating a product within minutes, the Multistate File to provide the excipient data required, and the List of Colorants to select rapidly the right color combination for worldwide acceptance of the product.

As well, special products like the DBCaps® can speed-up double-blind clinical trials on a global level, and the company's involvement with the Biopharmaceutics Classification System and PK/PD modeling is helping to establish clear development guidelines for product variations, generics or line extensions.

With its continual development of patented new products and technologies like the Licaps®/LEMS and the Press-Fit™, Capsugel is addressing the major challenges which the pharmaceutical industry is facing today, and offering practical solutions. With its recent alliances and acquisitions Capsugel is building a technology platform to better fulfil the needs and requirements of the development and production of pharmaceutical products and, more importantly, intends to continue its efforts to fulfil customer expectations.