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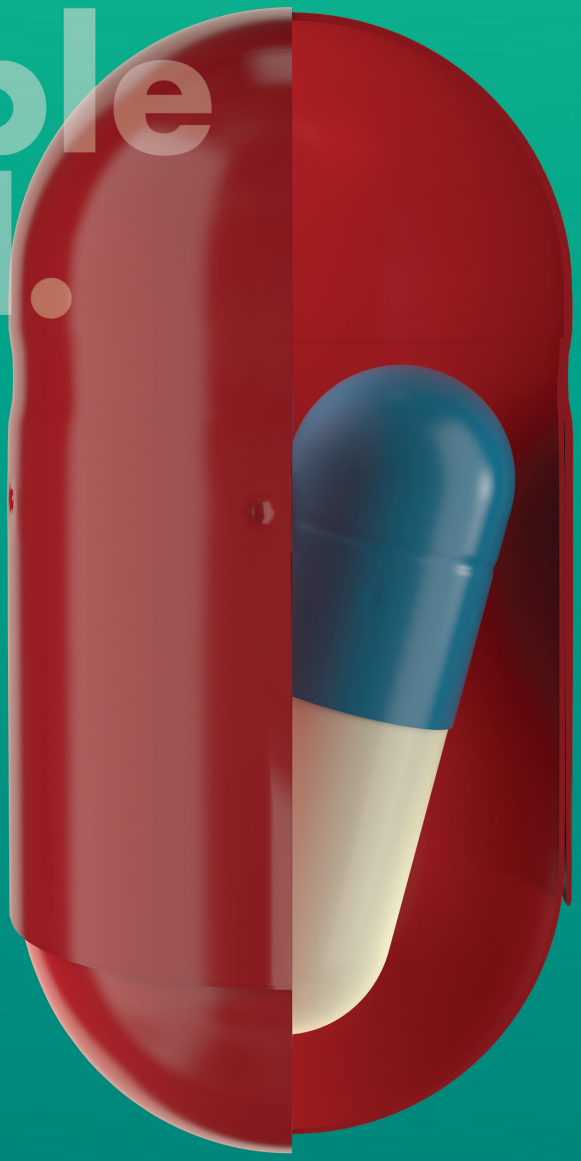

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DBcaps® capsules

Considerations in support of achieving successful double blinding and removing bias with over encapsulation

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Considerations in support of achieving successful double blinding and removing bias with over encapsulation

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Introduction

During the preparation of clinical studies, the method for visually blinding the dosage form is a decision that needs to be made early on in the process. The European Commission's Volume 4 Good Manufacturing Practices Annex 13: Manufacture of Investigational Medicinal Products (July 2003, updated February 2010), and the FDA's 21 CFR Part 211 provide the regulatory framework for the use and qualification of comparative agents in clinical trials.

GMP compliance requires:

- Provision of data to show that product quality has not been altered
- Justification of expiry dating
- Blinding that resists tampering and clearly reveals when tampering has occurred
- Rapid unblinding to identify the product in case of emergency.

While there are many blinding options available, over-encapsulation remains the most popular method adopted by sponsors to meet regulatory demands due to its relative simplicity. See table one.[1]

Despite the relative simplicity of over-encapsulation, proper planning and careful execution are still fundamental to success—full consideration must be given to every detail from capsule color and size selection to having a well-trained team dedicated to the process.

DBcaps® capsules

The most convenient capsule shell for blinding is the DBcaps® capsule. This type of shell is typically shorter and larger in diameter than the standard capsule shell sizes, making them easier for patients to swallow, helping to improve patient compliance.

An additional feature of this style is the double layer of shell that is created upon closing the capsule. This is due to the walls of each piece of the shell being almost identical in length. There is little area for the patient to grab a hold of at either end of the capsule, making it very difficult for the patient to pull the capsule apart. These two features not only make the capsule more user friendly from a manufacturing standpoint but assist in keeping the drug blinded at the patient level and create an anti-tampering measure.

[1]*Pharmaceutical Outsourcing, "Qualification Strategies for Blinded Comparators: One Company's Perspective", Karen Back-Moore (March 1, 2011): https://www.pharmoutsourcing.com/Featured-Articles/37894-b-Qualification-Strategies-for-Blinded-Comparators-b-p-One-Company-s-Perspective/. Accessed 16th July 2020.*

Table One: Blinding option availability

OPTION	ADVANTAGES	DISADVANTAGES
Over encapsulation	• Applicable to most capsule products and especially for ink logo capsules • Applicable to both very large and very small batch sizes • Preparation of matching placebo is a simple process • May accommodate unique tablet shapes • Applicable to most tablets and especially to debossed tablets and inked logo tablets • Can possibly generate new dose levels by adding multiple tablets to capsule if tablets are sufficiently small	• Commercial dose may not fit into capsules • Resulting capsule size may be too large for pediatric or geriatric studies
Removing ink logo from commercial products	• Most inks easily removed • No changes to existing analytical methods for the product are needed	• Requires confirmation of absence of residual solvent • Logo removal is a slow, manual and labor intensive process more suited for small batch sizes • Resulting capsule shell color may be difficult to match • Faint staining of residual ink on gelatin can be an issue
Re-coating active capsule	• Size of commercial dose does not noticeably change • Preparation of matching placebo is simple • Coating blinds both capsule color and ink logo on capsule shell	• Aqueous coating of gelatin capsules requires process development to minimize adverse effects of water on hard gelatin shells
Re-encapsulating powders	• Can easily match placebo to active • Can provide other dose levels if needed by changing fill weight • Concern with inked logo is eliminated	• Possible uniformity issues from segregation • Requires some process development • May not be suitable for products containing mixed controlled release beads or granules
Compressing powders	• Can provide other dose levels where required • Preparation of matching placebo is relatively simple • Concerns with color matching capsule shell or ink logo are eliminated	• Possible uniformity issues from segregation • Not appropriate for capsules containing functionally coated materials • Requires significant process development and analytical development • Resulting product may no longer be considered an equivalent commercial product and may require clinical bridging studies

Primary considerations for over encapsulation

For clinical conditions in which early exposure to the drug is a critical determinant of efficacy, and when encapsulation is used as a blinding method, it is strongly suggested that both the investigational and the reference drug are encapsulated so that appropriate comparisons and conclusions can be drawn

It is important to select the appropriate components that will be needed to support the over encapsulation of the tablet or capsule unit and plan ahead to curtail problems that could occur once the patient receives the supplies. This includes common challenges such as managing the shadowing' effect, where the dosage form is visible through the shell of the capsule, ensuring a consistent weight and feel, selecting an appropriate inactive backfill present in the dosage form that prevents 'rattling'.

Size

Once the unit has been identified, the first thing to determine is what size capsule shell will need to be utilized to properly blind each unit. Although it is not completely necessary, it is recommended that the unit that is being encapsulated does not protrude above the body of the capsule shell when inserted. If the unit does not "sit" properly inside the body shell, and backfilling is required, it may become necessary to backfill the capsule in a manner that will produce a considerable amount of backfill as waste.

When tablets are broken, it is critical to ensure that all of the tablet fragments are collected and accurately placed into each associated capsule shell. If all of the fragments are not collected, the final dose of the blinded tablet could be altered. In addition, in some markets it is not recommended by regulators to break tablets to fit them inside capsules for blinded clinical trials as there are questions raised around the impact this could have on drug efficacy and safety. For example, in the late 1990s regulations changed meaning that tablets could only be broken if they had been designed with a score and the developer had specifically conducted studies around the potential impact of this. This then needs to be included in the filing. This in turn led to an increase in demand for more flexible products for blinding studies.

Study populations are also a vital consideration as child and geriatric populations may have difficulty swallowing larger size capsule shells.

Color

The color of the capsule is an extremely important detail that requires a lot of insight. It is critical to choose a color that will completely hide the enclosed unit. The ideal color is one that does not show any shadowing or air pockets due to the backfill encompassing the unit, or allow for the encapsulated tablet or capsule to be seen. Ideally capsules for over encapsulation are generally opaque capsules in nature and are usually not the same color or shade of the unit being blinded, but rather slightly darker or more opaque in color.

It is vital that the capsule color will effectively blind the enclosed unit, but also that the color dyes and pigments used in the color formulation are accepted wherever the study is being conducted. Many countries have restrictions on particular colors or the total number of capsules. This needs to be researched prior to selecting a color.

Storage

Upon receiving the capsule shells, storage becomes an important issue. Be sure that the capsules are stored under the manufacturer's recommended temperature and humidity conditions.

Selection of backfill material

Backfilling the capsules is required to eliminate the rattle of the unit inside the capsule shell so that the patient is not able to determine the presence of another dose inside the capsule. If the rattle is not eliminated, the patient can possibly break the blind. In rare cases, backfill may not be used and both the placebo and the active doses contain over encapsulated units for similar rattle between the doses.

When selecting a backfill material, it is best, to choose an excipient that is present in the dosage form being blinded.

Dissolution profiles and stability work should be conducted to verify that the material selected does not interfere with or create any bioavailability issues in the over encapsulated dosage form.

The most commonly used excipients for backfilling are Microcrystalline Cellulose and Lactose Monohydrate. These materials are used both independently of one another as well as combined in a blend. In some cases, research has shown that the combination of the two may improve the dissolution results.

Depending on the grade of the material chosen, a lubricant, usually, Magnesium Stearate, present usually less than 0.5%, is added as part of the backfill formulation. Not all grades of these two materials require such lubrication and the choice of adding the Magnesium Stearate is usually based on its presence in the formulation of the unit being encapsulated.

Gelatin or HPMC

Gelatin-based capsules offer traditional benefits and are backed up with data to prove compatibility, but they do not meet clean-label requirements – being free from animal proteins or with colorings derived from natural sources.

Developers of therapeutics of all kinds are responding to emerging social and cultural trends. These include increasing consumer demand for products free from any animal proteins and with colors and ingredients derived solely from natural sources.

Hydroxy Propyl Methyl Cellulose (HPMC) based capsules show great potential in becoming the best-practice alternative to gelatin-based formulations, not only because of their provenance but performance as well. Further benefits include circumventing the regulatory burden of working with animal derivatives and global market acceptance for multi-center studies.

HPMC-based capsules are widely preferred in clinical trials, and for many investigational New Molecular Entities (NMEs), because they have the added flexibility to accommodate a vast array of drug products and formulations.

With potent NMEs under development, challenges deploying APIs in gelatin-based capsules are contributing to a shift towards the use of HPMC-based capsules. Issues with cross-linking reactions and difficulty containing hydroscopic APIs head the list of these challenges.

Benefits of HPMC as a base material:

Offers higher moisture tolerance which helps stabilize formulations and mitigates the challenges associated with APIs and excipients that are incompatible with gelatin.

Polymers can withstand a wider range of temperature variation and fluctuation in storage and transit, meaning there is less chance for brittleness or breakage when compared to traditional gelatin-based capsules.

Storage

Upon receiving the capsule shells, storage becomes an important issue. Be sure that the capsules are stored under the manufacturer's recommended temperature and humidity conditions.

DBcaps® capsules

Often specified for over-encapsulation of active comparators in double-blind clinical trials. The complete line of these specially designed capsules offers increased patient compliance. In addition, they feature a unique locking mechanism, providing unsurpassed protection from bias caused by breaking the blind.

HPMC-based capsules

The DBcaps® capsule product portfolio includes both gelatin and HPMC (vegetarian). This makes them suitable for use with hydroscopic molecules and molecules prone to cross-linking with gelatin, negating issues with the dissolution properties.

Capsugel® HPMC capsules disintegrate and release their contents independent of pH levels, ensuring immediate release.

HPMC capsules not only offer mechanical stability for manufacturing, they also offer excellent formulation stability that eliminates compatibility risk issues and helps drug formulators accelerate development timelines.

Lonza Engine™ equipment portfolio: Providing a complete solution for clinical trials with DBcaps® capsules

At Lonza Capsules and Health Ingredients, we also offer our own line of equipment for both filling and sealing capsules – Lonza Engine™ equipment portfolio.

Specific to DBcaps® capsules and the Lonza Engine™ equipment portfolio, the Capsugel® Ultra III™ capsule filling machine(CFM) is a cGMP-compliant capsule filling machine with innovative and flexible design options to meet a wide array of filling needs, including the ability to run our full line of DBcaps® capsules. When the Capsugel® Ultra III™ capsule filling machine(CFM) is used in conjunction with the Capsugel® TFR 8 Tablet Ring, which can be custom designed based upon request, tablets can be more easily inserted into capsules thereby helping to facilitate the over-encapsulation process.

Conclusion

Over-encapsulation is one of the simplest solutions for blinding solid oral dosages in comparative clinical trials. Its simplicity combined with high efficacy means it will be widely used throughout clinical trials for years to come.

Consideration must be given to the capsule's compatibility with encapsulated products - dissolution, diffusion and stability studies are essential elements of selection. Patient-centric efforts of manufacturers and trial sponsors have forged a path for innovative clean-label products in the form HPMC-based capsules compatible with vegetarian and vegan lifestyles. HPMC-capsule offer a range of development benefits that complement traditional hard-gelatin capsules, this increases accessibility to capsules for sponsors and gives them greater flexibility and product compatibility when selecting their dosage format.

Sponsors and clinical supply, manufacturing and service partners that understand and control every step of over-encapsulation—from material selection to manufacture—will leverage a simple, efficient means to ensure the integrity of their study and avoid bias.

DBcaps® capsules Double blind. Zero bias.

Available in several globally accepted colors, eight sizes and designed for double-blind clinical trials, DBcaps® capsules reduce clinical trial cycle time, without compromising quality and accuracy.

With several innovative design features that uniquely support reduced trial time and improved data integrity, DBcaps® capsules are the perfect choice for clinical trials. An invaluable asset for the clinical trial professional, DBcaps® capsules offer a long list of unique benefits, including:

Rapid blinding without altering
DBcaps® capsules wide diameters and range of sizes accommodate large and uniquely shaped tablets, caplets, as well as other capsules. By eliminating the need for modifying investigational as well as reference products, the testing requirements for stability and bioequivalence may be significantly reduced and the clinical trial design simplified.

Compatibility with challenging dosage form formulations
The range includes both gelatin and HPMC (vegetarian) variations. This makes suitable for use with hydroscopic molecules and molecules prone to cross-linking with gelatin, causing issues with the dissolution properties.

Unique locking mechanism
The elongated cap closes tightly with the body to help reduce the occurrence of trial participants opening the capsule and breaking the blind.

Facilitates ease of swallowing
The shortened overall length of DBcaps® capsules makes swallowing easier, thus encouraging patient compliance.

High-speed production capability
DBcaps® capsules can be filled on virtually all conventional high-speed filling machines, as well as on Lonza's own compact semiautomatic machines. Technical assistance on the filling of DBcaps® capsules is available from Lonza.

Globally approved color selection
DBcaps® capsules are available in eight sizes and several globally approved colors.

Author Biographies

Stephen Rode, B.S, G.B.A., Pharmaceutical Business Development Manager
Lonza Capsules and Health Ingredients

Currently, Steve is Manager of Business Development for Lonza's Capsules and Health Ingredients group and is focused on supporting and growing the pipeline of new pharmaceutical and OTC products, utilizing Lonza's diverse portfolio of capsule-based products and technologies. Steve received his B.S. in Agronomy from Pennsylvania State University in 1980 and a G.B.A. in Executive Management from The Wharton School at the University of Pennsylvania in 1988.

With more than 31 years of industry experience, Steve has had the privilege of working with many top pharmaceutical and consumer healthcare companies in the development and launch of pivotal products. In addition to Steve's sales and business development responsibilities, he has also had the opportunity to actively participate on various internal project teams. These include the development of DBcaps® capsules specifically for use in double-blind clinical trials, Vcaps® Plus HPMC capsules, and Coni-Snap® Sprinkle capsules for pediatric and geriatric drug delivery applications.

Frédérique Bordes-Picard, M.B.A., MSc, Business Development Manager, Innovative Products
Lonza Capsules and Health Ingredients

A biochemical engineer by training (Bordeaux Polytechnic Institute), Frédérique also holds a Master of Business Administration from KEDGE Business School. Frédérique has been working in the pharmaceutical industry for more than 20 years: first at AstraZeneca UK, working on analytical development of therapeutic proteins and antibodies, then at CDMO Bertin Pharma (now Eurofins), working mainly on generic product development and licensing out.

Frédérique joined Capsugel® in 2010 as Pharmaceutical Business Development Manager, providing technical and regulatory support for new capsule-based product developments. Frédérique has developed specific expertise around capsule-based DPI product development and filing, supporting multiple companies in the EMEA and United States by working on innovative products.

Julien Lamps, Product Manager
Lonza Capsules and Health Ingredients

Julien Lamps graduated from Ecole Nationale Supérieure de Chimie de Lille with an Engineering degree in Chemistry in 2004. Julien joined Capsugel as a Quality Assurance Engineer in the Colmar plant in 2011. In this role, he worked at the interphase of operations and customers within the well-known Capsugel® Quality Mindset. During this time he specialized in coordinating new product introductions to develop innovative offers around modified release profiles and inhalation products.

Julien is now Product Manager for Lonza's Capsules and Health Ingredients business unit, focusing on inhalation and HPMC portfolios.

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