Capsugel®

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Reduced Risk and Faster Time to Market with Sigma Quality Hard Capsules

Risk associated with scale-up should be considered in control strategy development to maximize the probability of effectiveness at scale.

FDA GUIDANCE

Over the past several decades, as the FDA has introduced a number of fast tracks for drug approval, pharmaceutical companies looking to take advantage of those pathways have increasingly chosen hard capsules over other dosage forms.

Between 2010 and 2014, the FDA approved over 20 encapsulated products through its Accelerated Approval, Fast Track, Breakthrough Therapy, and Priority Review programs. As a result, patients suffering from devastating conditions such as lung cancer, multiple sclerosis, and Hepatitis C got speedy access to life-saving new medications.

Pharmacyclics' oncology drug Imbruvica, Boehringer Ingelheim's anti-coagulant Pradaxa, Novartis's Gilenya for multiple sclerosis, and Intermune's Esbriet for idiopathic pulmonary fibrosis are among the capsules approved through these programs in the past few years.

With the launch of Capsugel's Coni-Snap Sigma Series in January 2014, the hard capsule dosage form option has become even more attractive to an industry looking to optimize development, manufacturing processes, and the supply chain. In Europe and the US, where the Sigma Series capsules have been available since the initial launch, interest has grown, with pharmaceutical companies reporting that the new level of quality allows them the peace of mind to focus on assuring the robustness of other aspects of their encapsulation processes.

Quality by Design considerations

Minimizing variability and defects in excipients, including empty capsules, has become an increasing priority for the pharmaceutical industry since the FDA introduced its Quality by Design (QbD) program, Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach, in 2002.

The initiative introduced revised current Good Manufacturing Practices (cGMP) that encouraged the industry to focus on reducing risk through improved control over critical product and process parameters. The revamped program emphasized the importance of leaving behind traditional methods of quality control that relied on testing completed products and discarding those that fail to meet specifications. Instead, the industry would shift its attention to assuring quality through proper process design and risk management.

In a 2007 progress report on the QbD initiative, the FDA explained that "The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks."

Both the FDA and EMA, developed guidances based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) quality guidelines Q8, Q9, and Q10, covering pharmaceutical development, quality risk management, and quality systems.

Both agencies also accept QbD-based applications, with the FDA receiving over 50 QbD-based NDAs and supplements by 2011. Since that same year, both agencies have participated in a parallel assessment program in which they make an effort to harmonize their evaluations of the portions of applications relevant to QbD, including development, design space and realtime release testing.

In developing QbD programs, manufacturers must take the impact of raw materials on the design space into account right from the start of the design process. The FDA's guidance on the ICH guidelines recommends that, "Risk associated with scale-up should be considered in control strategy development to maximize the probability of effectiveness at scale," including differences in raw material quality due to batch-to-batch variability and the "impact of such differences on process controls and quality attributes."

If there is any evidence of variability in the raw materials that may affect results from the design of experiments, the guidance notes, sponsors may need to include information about the potential impact in a QbD regulatory submission. Obviously, raw materials, including empty hard gelatin capsules, with variability small enough to avoid any significant impact on critical product or process parameters may help to avoid complications in the establishment of a design space and in obtaining regulatory approval.

Transitioning from AQL to PPM standards

As QbD efforts took hold throughout the pharmaceutical industry, Capsugel undertook an initiative to further tighten controls in its own manufacturing facilities, in order to produce capsules with defect levels so low as to be undetectable by standard sampling methods, an unprecedented level of quality.

In 2014, as a result of that initiative, Capsugel introduced gelatin capsules under a new framing reference, Coni-Snap Sigma Series hard gelatin capsules, which are manufactured to Six Sigma quality levels. Six Sigma quality means that instead of defect levels defined by the industry standard limit, Acceptable Quality Level (AQL), which could allow hundreds of defects per million capsules, Sigma Series defects do not exceed 3.4 parts per million (ppm).

The most stringent requirements set out in the American National Standards Institute (ANSI) AQL tables specify an AQL of 0.01% nonconforming items. Since Capsugel typically produces batches of empty capsules in the range of 10-20 million per lot, and ANSI calls for maximum sample sizes of 2,000 pieces for lots of 500,000 and over, the level of defects in a lot of Coni-Snap Sigma Series falls well below that which is detectable by AQL.

Initially, some manufacturers expressed concern about transitioning to the Sigma Series line due to regulatory requirements regarding sampling of the capsules; however, because Capsugel is continuing to sample outgoing product and providing outgoing AQL information, no regulatory filing is necessary. To support new regulatory submissions, Capsugel has submitted excipient drug master files (DMF) for all of its products, and sponsors may obtain a letter of authorization to refer to a DMF.

In Europe and the US, where the Sigma Series capsules have been available since the initial launch, acceptance has been rapid, with pharmaceutical companies reporting that the impressive level of quality allows them the peace of mind to focus on assuring the robustness of other aspects of their encapsulation processes.

In fact, US and European customers have adopted the new line of capsules so readily, says Ronny van de Neste, Global Director of Capsugel's hard capsule business, that they have been asking for access to Sigma Series capsules for their Asian encapsulation facilities; Capsugel is responding by expanding the manufacture of Sigma Series to its Chinese plant.

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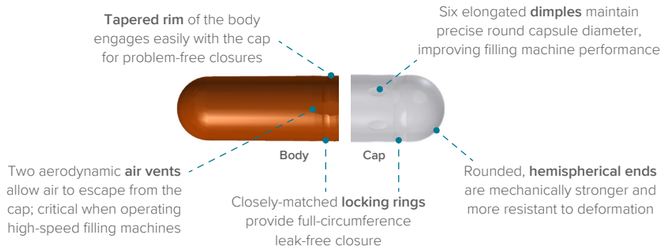
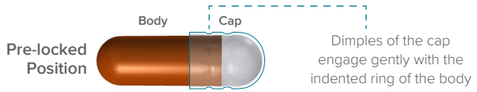
JOHN DAVIDSON
SENIOR MANAGER, QUALITY ENGINEERING SERVICES, CAPSUGEL

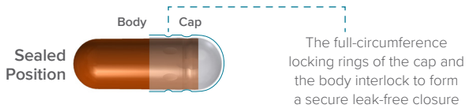
CONI-SNAP® SIGMA SERIES CAPSULES IN GELATIN AND HPMC

Patented pre-lock and locking design is the standard for quality in the industry





Empty capsules stay closed in transit; yet the consistent low pre-lock force reduces opening and rectification problems



Speeding time to market

For most manufacturers, Sigma Series capsules offer the potential to improve efficiency throughout the supply chain by minimizing delays and by reducing time required for acceptance testing, processing, and release, all without any need for regulatory filings or changes to the encapsulation process.

For starters, the superior quality of Sigma Series capsules gives many companies the confidence to participate in a certified vendor program, significantly reducing the time and cost of testing incoming batches. Companies participating in this program test a limited number of parameters themselves and rely on results included in the certificate of analysis (CofA) for the remainder, as allowed by cGMP regulations.

“The guarantee that we are achieving defect levels far below that which sampling could detect,” says John Davidson, Senior Manager of Capsugel’s Quality Engineering Services Team, “is an opportunity to eliminate some of that testing because there is no longer a rationale for it, so once the quality control personnel receive the material, they can release it to their operations group very quickly.”

Once the capsules are put into production, the extraordinarily low level of defects also gives operations personnel the assurance that observation of a single capsule with a small defect almost certainly represents an isolated incident, avoiding a production shut down and quarantine of a batch, a source of delays that has become more common in recent years.

Davidson explains that as manufacturers have become more sensitive to risks posed by even minor visual and print defects, the burden of proof of on quality control to show acceptability has grown, along with the response time and labor required to deal with the risk: “As the years have gone on, our customers are responding to defects that they might have accepted before such as cosmetic blemishes on the capsule, by generating deviation reports or undertaking internal investigations, so today defects are generating more paperwork and more product is being stuck in a quarantine status.”

All of that analysis and paperwork can take up to 30 days, Davidson adds, and quarantining both the filled and empty capsules during the course of an investigation can seriously disrupt the entire supply chain.

Even just eliminating the capsules as a factor in a defect investigation simplifies the job for operations personnel and reduces pressure on the supply chain, Davidson notes: “They still might have to investigate defects observed during encapsulation, but it won’t be because of raw materials.”

Ensuring Confidence in Critical Attributes

VISUAL AND PRINT QUALITY

As the pharmaceutical industry has implemented QbD efforts in recent years, variations in capsule attributes such as imprint legibility, capsule weight, dimensions, and moisture have become an even greater concern.

Imprint quality is a particularly critical attribute because, as an FDA guidance titled “Safety Considerations for Product Design to Minimize Medication Errors” points out, “Imprint codes that are absent, difficult to see, and similar to imprint codes of another product have led to the dispensing and administration of the wrong drug product and wrong strength.”

In 21 CFR 206, The FDA spells out the requirement for clear imprints, specifying that “no drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product’s size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product.”

Beyond the safety risks posed by missing or illegible imprints, there is the risk that patients who observe visual or print defects may question the legitimacy of the product and/or file a complaint. Over the past few years, consumers have been exposed to an increasing number of reports on counterfeit drugs in the media. Many of these reports warn consumers that capsules whose imprint and/or color differ from normal could be fake, and social media can amplify these worries.

Online resources also reinforce the message that consumers should be wary of capsules with print defects. Drugs.com, for example, warns consumers that “A solid oral dosage form drug product that does not meet the requirement for imprinting and

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SENIOR DIRECTOR FOR GLOBAL QUALITY, CAPSUGEL

is not exempt from the requirement may be considered adulterated and misbranded and may be an unapproved new drug as defined by the FDA. Also, if a pill or capsule has no imprint and is not an approved medication it may be a vitamin or other dietary supplement, illegal drug of abuse, foreign medication or even candy.”

With the proliferation of drug identification websites and mobile apps, patients have easy access to images showing how the imprint on their capsules should appear, and online message boards offer numerous examples of users inquiring about capsules they have found that lack imprints.

For many patients, visual and print quality also correlate to overall product quality, making the capsule appearance particularly important from a product differentiation standpoint. Misprinted logos, color hue errors, or sloppy edges on a cap have the potential to negate the effect of the company’s careful choice of logo and colors to represent the brand.

At Capsugel’s high production speeds, assuring perfect imprints requires extraordinarily tight control of the offset printing process used to mark capsules. Even a tiny speck of dust on an ink roller for just a couple of seconds could result in missing print or a thick line that obscures the logo on as many as 10-20 capsules. Those defects would be difficult to detect and eliminate through sampling of lots that may include 20 million capsules.

In order to bring its capsule printing processes to Six Sigma level quality, Capsugel closely studied its printing systems and then re-engineered the entire process for greater control over ink application and imprint placement, replacing 20% of the ink rollers, and instituting 100% electronic inspection.

In addition to assuring imprint quality and playing a role in lowering the print defect rate to no more than 3.4 ppm, 100% inspection also drastically reduces other potential visual quality issues such as poorly distributed pigment in colored capsules, specks, and pits.

WEIGHT, DIMENSIONS, AND OTHER PARAMETERS

As part of its commitment to continuous quality improvement, Capsugel performed a study of critical parameters from 42 batches of size 1 capsules manufactured over a 24-month period. Half of the batches were transparent capsules; the remaining batches were opaque white capsules.

Results from the study were published an article titled, “Application of QbD Principles for the Evaluation of Empty Hard Capsules as an Input Parameter in Formulation Development and Manufacturing” in the June 2014 issue of the journal AAPS PharmSciTech.

The study paid particularly careful attention to two of the most critical parameters, capsule weight and dimensions. Variability in capsule weight may have a critical impact on product performance due to its effect on *in vitro* parameters such as dissolution and disintegration. For low fill weight products such as dry powder inhaler capsules, variation in capsule weight may also result in a significant variation in the amount of drug dosed.

If manufacturers receive capsules with significant dimensional differences, they might need to make adjustments to encapsulation equipment to avoid downtime. Variations in dimensions might also cause defects such as dented capsules or a poor fit between the two halves of the capsule that may result in leakage. Ensuring that capsule dimensions remain within specifications becomes particularly critical on high speed filling machines that handle up to 250,000 capsules per hour.

With all Capsugel capsules, says Karin Schrooten, Senior Director for Global Quality, customers can rest assured not only that the variation in capsule parameters remains well within specifications for each lot of empty capsules, but also that dimensions and weight remain consistent enough from lot to lot to allow manufacturers to switch lots without having to make any adjustments to the encapsulation equipment.

”We can provide the customer with data showing that our process is very capable and that capsule weight or specifications will be within very tight ranges so customers know that if they buy a capsule batch now and then buy a batch six months later, it’s not going to impact them,” she adds.

For example, the target weight for a size 1 capsule, the size most commonly used in the pharmaceutical industry, is 76 mg, with an allowable range of +/- 5 mg. Data from the Capsugel study showed that the overall weight distribution of the batches, based on the average weight of 100 capsules, varied between 73.4 and 76.7 mg, with individual capsule weights well within limits. No difference in weight distribution was observed between transparent and colored capsule batches.

For dimensional parameters including cap and body length, the study showed that measurements stayed well within the specification limits over the two-year period with little variation between the 42 batches of capsules. For both weight and dimensional parameters, the relative standard deviation was calculated at about 2%.

Measurements of additional critical quality attributes – moisture, disintegration, sulfated ash, sulfur dioxide, lubricant, and microbiology – demonstrated that all easily met pharmacopoeial requirements with tight control both within batches and between batches.

With such tight control, Capsugel experts have added ability to assist customers in determining how capsules variation within specifications will affect production and/or the end product. “We can work together with the customer to help them define what the best conditions are for the product and what they need in order to define their design space,” Schrooten says.

Continuing Innovations in Quality

The introduction of the Coni-Snap Sigma Series line might represent a great advance in the quality of empty hard gelatin capsules, but it’s just a single step in Capsugel’s ongoing program of quality improvement.

“We have been working over the past 20 years on continuous improvement,” Van de Neste says, “on developing new production technologies other than inspection, to design and engineer out the root causes for defects, and so we have over all these years continued to lower the defect levels in our product.”

That effort is ongoing and will continue indefinitely, he adds, with the company’s sights set on bringing six sigma quality to additional regions, parameters, and products, including its Vcaps® Plus HPMC capsules. On its website, Capsugel indicates that it will not settle for anything less than the ideal: “Our ongoing commitment to Six Sigma leads us onwards and upwards towards the ultimate goal of zero defects.”

Capsugel®

FOR MORE INFORMATION CONTACT US AT
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