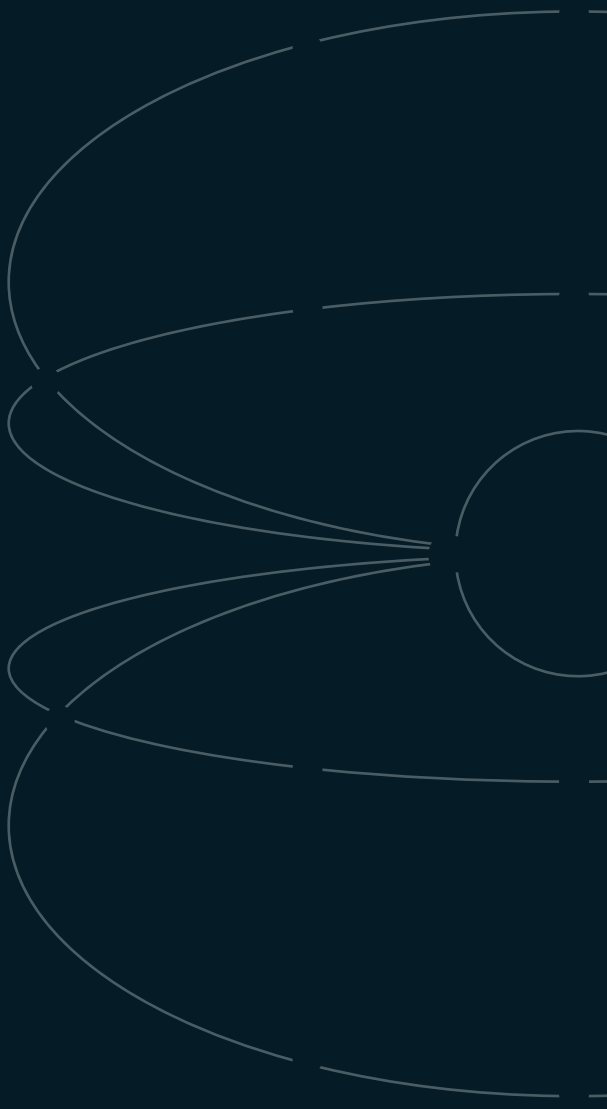
Forma

Five Ways to Position a 505 (b)(2)

Five proven strategies.
Clinically meaninful differentiation.
Stronger 505(b)(2) products.



Five Ways to Position a 505(b)(2)

There are five primary ways to position a 505(b)(2): change the route of administration or dosage form, reshape the dosing regimen, combine established active ingredients, reduce food or gastric pH dependence, or engineer a safety feature into the dosage form.

We, at Forma, reviewed prominent products across each strategy to understand what made them meaningfully differentiated and which formulation technologies enabled that differentiation. Together, these examples highlight the formulation approaches best suited to developing clinically meaningful and commercially differentiated 505(b)(2) products.

1. Change the Route of Administration or Dosage Form

This strategy uses buccal, sublingual, nasal, pulmonary, or other alternative delivery formats to increase exposure, avoid gastrointestinal degradation or first-pass metabolism, accelerate absorption, or enable local delivery. The formulation must be designed around the available fluid volume, absorption surface, residence time, and mechanical constraints of the new administration site.

SYMPAZAN Oral Film

SYMPAZAN contains clobazam and is approved as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patients two years of age and older. The 505(b)(2) application relied in part on FDA's prior findings for ONFI but introduced an oral-film formulation designed to provide the same active ingredient in a dosage form that dissolves directly on the tongue.

The product consists of a thin, water-soluble polymer matrix containing Hypromellose and Polyethylene oxide, with Clobazam distributed throughout the film. Unlike a compressed tablet, the dose is defined by drug loading per unit area, film thickness, casting uniformity, and cutting precision. The matrix must remain mechanically robust through web handling, printing, cutting, packaging, and pouch removal, while hydrating rapidly in the limited fluid volume available in the oral cavity.

Performance depends on polymer ratio, plasticization, solution rheology, drying rate, residual moisture, film thickness, and control of drug migration during drying. These variables influence tensile strength, flexibility, disintegration, and unit-dose content uniformity. The film therefore functions as a continuous drug-loaded matrix in which mechanical properties, dimensional control, and hydration behavior collectively determine manufacturability and in-use performance.

Source: CDER Clinical Reviews, application number 210833Orig1s000

2. Reshape the Dosing Regimen

This strategy uses delayed-release, extended-release, pulsatile, or chronotherapeutic systems to control when release begins and how it progresses. Multiparticulate systems are especially useful

because multiple release functions can be built into sequential coatings or distributed across separate particle populations.

JORNAY PM

JORNAY PM contains Methylphenidate and is approved for ADHD in patients six years and older. The 505(b)(2) application relied in part on FDA's prior findings for Ritalin but introduced an evening-dosed formulation designed to suppress methylphenidate release overnight and provide exposure beginning the following morning.

The capsule contains drug-layered multiparticulate beads surrounded by two functional film coatings. The outer delayed-release coating controls the overnight lag period, while the inner extended-release coating regulates the subsequent release rate. This sequential architecture separates the two formulation functions: the first membrane population determines when release begins, and the second determines the duration and shape of the release profile.

Performance depends on coating composition, coating weight gains, membrane permeability, plasticizer concentration, pore formation, curing conditions, and bead-size distributions. The outer membrane must remain sufficiently impermeable during the lag phase without damaging or prematurely plasticizing the inner layer. Once fluid penetrates the delayed-release barrier, the inner membrane must provide reproducible diffusion-controlled release across thousands of individual beads. The multiparticulate design also distributes the dosage form throughout the gastrointestinal tract, reducing reliance on the erosion or transit behavior of a single monolithic tablet.

Source: CDER Clinical Reviews, application number 209311Orig1s000

3. Combine Established Active Ingredients

This strategy combines previously approved active ingredients in one dosage form while preserving the formulation environment and release profile required by each component. Bilayer tablets, separately granulated components, coated pellets, and MUPS systems can provide physical separation when the APIs differ in stability, dose, particle properties, or release requirements.

AUVELITY

AUVELITY contains Dextromethorphan and Bupropion and is approved for major depressive disorder in adults. Dextromethorphan and Bupropion were both previously approved active ingredients, but AUVELITY combines them in a single extended-release 505(b)(2) product.

The product is a film-coated bilayer tablet containing immediate-release Dextromethorphan and extended-release Bupropion. The bilayer architecture provides separate formulation environments within one dosage form, allowing the two components to use different excipient systems and release mechanisms. It also limits direct API-to-API contact areas and allows the immediate-release and extended-release portions to be manufactured and controlled independently before final compression.

Bilayer manufacturing introduces constraints that are absent in a conventional monolithic tablet. The first layer must retain sufficient porosity and surface characteristics to bond with the second layer but also withstand the second compression event without overcompaction. Layer weight, granule size, flow ability, lubricant distribution, first-layer tamping force, final compression force, dwell time, elastic recovery, and interfacial contamination all influence layer adhesion and the risk of delamination during coating, packaging, and storage.

A multiparticulate alternative would place the active ingredients, or their respective release fractions, into separately manufactured pellet populations. Each population could be independently drug-layered and functionally coated before being blended into a capsule or compressed into a MUPS tablet. This approach provides greater flexibility when the APIs require incompatible processing conditions or independently adjustable release profiles.

Source: CDER Clinical Reviews, application number 215430Orig1s000

4. Reduce Food and Gastric pH Dependence

This strategy uses amorphization, particle engineering, precipitation inhibition, or other solubility-enabling approaches to reduce absorption variability caused by food intake or acid-suppressive therapy. The formulation must increase dissolution under unfavorable gastrointestinal conditions while preventing rapid recrystallization or precipitation after the drug enters solution.

CAVHANZA

CAVHANZA contains Nilotinib and is approved for adults with Philadelphia chromosome-positive chronic myeloid leukemia. It was developed through 505(b)(2) as an orally disintegrating alternative to conventional Nilotinib capsules, which have clinically important food restrictions and pH-dependent absorption.

CAVHANZA uses ElectroNanoSpray technology to produce fine amorphous Nilotinib-HPMCAS particles. In the electrospray process, a drug-polymer solution is subjected to a high electric field that forms small charged droplets. Rapid solvent loss converts those droplets into amorphous solid-dispersion particles on the micron or submicron scale. The process provides direct control over particle size, morphology, drug loading, and the distribution of Nilotinib within the polymer phase.

The formulation combines three related mechanisms. Amorphization removes the crystal-lattice energy that must be overcome before dissolution. Fine particle formation increases the available interfacial area and shortens the diffusion distance through the particle. HPMCAS stabilizes the amorphous drug during storage and inhibits recrystallization after dispersion in intestinal fluid, allowing the system to generate and maintain supersaturation. Together, these properties make Nilotinib dissolution less dependent on meal-associated solubilization or a strongly acidic gastric environment, reducing the food effect and permitting administration with common gastric acid-reducing agents.

https://patents.google.com/patent/US11998548B2

5. Engineer a Safety Feature Into the Dosage Form

This strategy uses the bulk physicochemical properties of the formulation to reduce a defined product-related risk. In abuse-deterrent products, the dosage form must preserve extended release during intended use while resisting crushing, milling, extraction, alcohol dumping, dissolution, insufflation, or preparation for injection.

HYSINGLA ER

HYSINGLA ER is a once-daily, single-entity hydrocodone tablet for severe pain requiring long-term opioid treatment. Its 505(b)(2) application relied in part on FDA's prior findings for Vicoprofen while introducing an extended-release formulation with physicochemical abuse-deterrent properties.

The tablet uses a high-molecular-weight Polyethylene oxide matrix that performs several functions simultaneously. During intended administration, water penetrates the matrix and hydrates the polymer, creating a swollen gel layer through which hydrocodone must diffuse. The progression of hydration, swelling, diffusion, and matrix relaxation controls extended release over the dosing interval.

The dense and heat-treated PEO matrix also provides substantial mechanical resistance. This type of tablet is difficult to cut, chew, or reduce to a fine powder using commonly available tools. When intact or manipulated material is exposed to water, the polymer absorbs fluid and forms a highly viscous hydrogel. That behavior complicates drug extraction, traps precipitated drug within the hydrated matrix and limits the ability to draw the preparation through a hypodermic needle.

These functions depend on polymer molecular weight, polymer degradation during processing, matrix density, API loading, porosity, tablet dimensions, compression conditions, and the distribution of polymer throughout the compact. Abuse deterrence is therefore embedded in the bulk structure of the tablet rather than applied as a secondary coating or external feature.

Source: CDER Clinical Reviews, application number 206627Orig1s000

How Forma's Technologies Map to the Five Strategies

The five case studies point to a relatively compact set of formulation architectures. Route and dosage-form changes require control of films, particles, or alternative delivery interfaces. Dosing-regimen changes require functional membranes or release-controlling matrices. Fixed-dose combinations require physical separation and synchronization of multiple components. Food and gastric pH mitigation requires control of solid state, dissolution, and precipitation. Abuse deterrence requires a matrix with coordinated mechanical, hydration, and release properties.

Forma applies four connected technology families to these problems: fluid-bed particle engineering, hot-melt extrusion, spray drying, and final dosage-form integration. The technologies do not map one-to-one with the five strategies. Each can be configured to solve several product-

design problems, and the appropriate platform is determined by the physical mechanism required to create the intended product profile.

Fluid-Bed Granulation and Functional Coating

Forma's Syntegon fluid-bed lines support granulation, drug layering, drying, powder layering and functional coating of powders, particles, and pellets. Conditioned process air fluidizes the material while spray nozzles apply drug solutions, binders, seal coats, or release-controlling polymers. Depending on the configuration, the process can build drug layers onto inert cores, granulate fine powders, or apply uniform functional membranes around individual pellets.

For multiparticulate modified-release products, release behavior is created at the particle level. An inert core may first receive a drug layer, followed by a protective seal coat and one or more functional membranes. Extended-release, delayed-release, enteric, or pulsatile behavior can be tuned through polymer chemistry, coating weight gains, membrane permeability, plasticizer concentration, pore formers, curing conditions, and pellet-size distributions.

Different particle populations can be designed independently and combined in defined ratios. One population may provide immediate release, another extended release, and a third a delayed pulse. This is the general architecture used in chronotherapeutic products such as JORNAY PM, where sequential coatings determine both the lag phase and the subsequent release rate.

The same approach is valuable for fixed-dose combinations. Chemically or physically incompatible APIs can be placed on separate pellet populations and exposed to different formulations and coating conditions. The populations are combined only during final blending, capsule filling, or MUPS compression, limiting direct API contact and allowing each component's release profile to be adjusted independently.

Multiparticulates also provide flexibility in the final presentation. Coated particles can be filled into capsules, packaged as sprinkles or sachets, dispersed into suspensions, or compressed into MUPS tablets. MUPS compression is particularly demanding because the tablet must achieve sufficient tensile strength without rupturing the functional coatings around the pellets. Pellet deformability, cushioning excipients, particle-size distribution, compression force, and elastic recovery must therefore be controlled as part of an integrated formulation and tableting strategy. Forma's tablet press platform specifically supports MUPS applications.

Hot-Melt Extrusion

Forma's Leistritz Hot-melt extrusion line of equipment uses thermal energy, shear, and continuous mixing to distribute an API within a thermoplastic polymer system. The extrudate may be milled into granules, cut or pelletized into multiparticulates, compressed into tablets, filled into capsules, or converted into a film. Polymer selection, drug loading, screw configuration, residence time, melt temperature, torque, and specific mechanical energy determine the structure and performance of the resulting intermediate.

For extended-release products, the API can be dispersed within a hydrophilic, hydrophobic, or erosion-controlled polymer matrix. Drug release is governed by water penetration, polymer

swelling, diffusion, erosion, and dosage-form geometry. Altering polymer grades, drug loading, plasticizer concentration, porosity, or extrudate dimensions provides a direct means of reshaping the release profile.

HME also supports pediatric formulations. Extrudates can be converted into small pellets, mini-tablets, or taste-masked granules that provide flexible dosing and reduced swallowing burden. The continuous polymer phase can restrict drug dissolution in saliva while permitting release after the product reaches the gastrointestinal tract. Research has demonstrated the production of hot-melt-extruded, taste-masked mini-tablets intended for pediatric and geriatric administration.

When coupled with appropriate film-forming and converting equipment, HME can produce drug-loaded polymeric films for sublingual, buccal, or orally dissolving delivery. The solvent-free process can provide precise control over drug-polymer mixing and film composition, while downstream calendaring, thickness control, cutting, and packaging determine the final unit-dose geometry. This makes HME relevant to the same dosage-form class illustrated by oral-film products such as SYMPAZAN, even though the manufacturing process selected for any commercial film is product-specific. Forma identifies sublingual systems as an application of its hot-melt-extrusion platform.

HME is also well suited to abuse-deterrent matrix systems. Thermally processed, high-molecular-weight Polyethylene oxide can combine extended release, resistance to particle-size reduction, and aqueous gelling. The resulting performance depends not only on formulation composition, but also on polymer degradation, thermal history, post-extrusion processing, and the density of the final compact. FDA research has specifically used hot-melt extrusion to prepare Polyethylene oxide-based abuse-deterrent tablets and evaluate the consequences of manipulation.

Spray Drying

Forma's Anhydro Spray drying line converts a liquid feed into dry particles through atomization and rapid solvent removal. The process provides control over solid state, particle size, morphology, density, surface composition, residual solvent, and powder flow. Feed composition, solvent system, solids concentration, atomization conditions, inlet and outlet temperatures, drying-gas flow, and collection conditions collectively determine the properties of the resulting powder.

For poorly soluble oral compounds, spray drying can produce an amorphous solid dispersion in which the API is molecularly or finely dispersed within a polymer matrix. Amorphization removes the crystal-lattice barrier to dissolution, while the polymer stabilizes the higher-energy solid state and inhibits precipitation after administration. The objective is not simply to make the drug dissolve faster in a compendial medium. It is to create and maintain a dissolved concentration that is less dependent on food-mediated solubilization or strongly acidic gastric conditions. Forma's spray-dried-dispersion platform includes polymer screening, feed preparation, solvent handling, atomization optimization, and amorphous particle engineering.

This makes spray drying directly relevant to food-effects and gastric pH mitigation. Conventional spray drying and ElectroNanoSpray use different atomization and drying mechanisms, but both can create engineered amorphous drug-polymer particles. The appropriate process depends on the compound's thermal sensitivity, solvent compatibility, target particle characteristics, scale, and downstream dosage form.

Spray drying also enables pulmonary delivery. For an inhaled product, geometric particle size alone does not determine performance. Lung deposition is governed by aerodynamic diameter, which incorporates particle dimensions, density, morphology, and dynamic shape. Surface composition, cohesiveness, moisture content, and dispersibility influence whether the powder exits the capsule, deaggregates in the inhaler, and reaches the intended region of the respiratory tract.

INBRIJA provides a useful 505(b)(2) precedent. It reformulated Levodopa from the oral Carbidopa-Levodopa product SINEMET into an inhalation powder for the intermittent treatment of OFF episodes in Parkinson's disease. The drug product contains spray-dried Levodopa, DPPC, and Sodium Chloride in capsules administered through a breath-actuated inhaler. Its control strategy includes emitted dose, delivered-dose uniformity, powder morphology, and aerodynamic particle-size distributions.

The same unit operation can therefore solve two very different product-design problems. In an oral amorphous dispersion, spray drying controls solid state and dissolution. In an inhaled product, it controls aerosolization and pulmonary deposition.

Final Dosage-Form Integration

The engineered film, pellet, extrudate, or spray-dried powder remains an intermediate until it is converted into a final dosage form that preserves its intended function. Forma's Korsch tableting line, Planeta capsule filling line, and Thomas Engineering coater lines provide the downstream infrastructure needed to integrate these materials into commercial tablets and capsules.

This stage is particularly important for complex 505(b)(2) products because final processing can alter the attributes created upstream. MUPS compression can rupture functional pellet coatings. Bilayer tableting can produce interfacial weakness or delamination. Spray-dried dispersions may compact poorly, absorb moisture, or recrystallize during processing and storage. Orally disintegrating tablets must balance rapid disintegration against friability, hygroscopicity, and packaging requirements. Capsule blends containing multiple particle populations must maintain content uniformity despite differences in size, density, morphology, and electrostatic behavior.

Final dosage-form development must therefore be treated as an extension of particle and material engineering rather than a separate packaging step. Excipient selection, blending order, lubrication, compression profile, coating conditions, environmental controls, and container-closure selection must all preserve the mechanism that creates the product's differentiation.

Matching the Formulation Architecture to the Product Strategy

The five strategies represent five different physical problems. Route and dosage-form changes determine where and how the drug is presented. Dosing-regimen changes determine when release begins and how it progresses. Fixed-dose combinations require separation and synchronization of multiple components. Food and gastric pH mitigation requires dissolution to be decoupled from gastrointestinal variability. Safety-enhanced formulations use material properties to resist an unintended mode of use.

The value of studying established 505(b)(2) products is not simply to catalogue what has already been approved. It is to identify which formulation architecture is best matched to each development objective. Polymeric films provide a route to new oral presentations. Functional coatings and multiparticulates allow release to be programmed at the particle level. Bilayers and MUPS systems preserve separate formulation environments within a fixed-dose product. Amorphous dispersions shift control of dissolution away from gastrointestinal physiology. High-molecular-weight matrices combine release control with mechanical and solvent-responsive properties.

A strong 505(b)(2) program aligns three elements around the same physical mechanism: the clinical differentiation being sought, the evidence required to bridge to the established product, and the manufacturing process capable of reproducing the formulation at commercial scale. Forma's fluid-bed processing, hot-melt extrusion, spray drying, and final dosage-form integration provide the technical ranges to select and scale that architecture from engineered intermediate through finished drug product.

About Forma

Forma Life Sciences is a U.S. based contract development and manufacturing organization (CDMO) specializing in oral solid dosage formulation development, clinical manufacturing, and commercial drug product manufacturing. Headquartered in Irvine, California, Forma operates two cGMP facilities totaling more than 100,000 square feet and 27 GMP manufacturing suites, with capacity to produce over two billion tablet and capsule units annually. The company supports pharmaceutical and biotechnology partners from early clinical development through commercial scale production and offers expertise in spray-dried dispersion, amorphous solid dispersion systems, fluid bed granulation, and modified-release formulation technologies.