



Designing a New Drug Package

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The process of designing a new drug package must follow specific steps to ensure low costs and rapid market approval.

When designing a package for a new pharmaceutical product, attention to detail is imperative, and there are many details to consider. The sequence of events is important also. If a step is overlooked or out of order, expenses can escalate dramatically, and there could be a delay to market with attendant losses of sales and market share.

As the packaging design process proceeds, design reviews should be conducted periodically to ensure the credibility of performance criteria, physical safety, compatibility, barrier demands, and manufacturability. The reviews can also resolve documentation issues such as assembly drawings, manufacturing instructions, testing strategy, and sterilization validation (1).

Every pharmaceutical company has its own package design process. Variations depend on the company's culture, size, staffing, and tradition. However, many manufacturers agree that the process has become more complicated in recent years.

First steps

The packaging design process should begin early in drug development. Designing a package begins with the dosage form. Once the dosage has been determined, one should become aware of any compatibility issues such as oxygen, moisture, or light sensitivity and any other idiosyncrasies that should be considered when developing the package. "It's essential to learn as much as possible about the entity's chemical background," says one packaging developer.

The chemistry of a new product typically is defined in the research department and should be available long before the start of stability studies. The research group also may do some cursory evaluations of material-product compatibility. Generally, the highest likelihood of product-package interactions occurs with inhalation aerosols and solutions and injections and injectable suspensions, followed by ophthalmic solutions and suspensions, transdermal ointments and patches, and nasal aerosols and sprays. In ad-

dition, topical solutions and suspensions, topical and lingual aerosols, and oral solutions and suspensions are prone to interactions. However, product-package interaction is less likely to cause concern with the latter dosage forms. At medium risk for interactions, but of high concern, are sterile powders and powders for injection and inhalation powders (2).

With the knowledge of the product's chemistry, a primary specification can be outlined in preparation for stability testing. Specifications typically follow one of two strategies. One strategy relies on a package structure with maximum barrier properties to guarantee that it will pass stability testing. The other strategy looks at several package variations with differing barrier characteristics with the goal of identifying a low-cost option that has sufficient barrier properties to ensure stability (3). Either scenario can result in high packaging costs during the life of the product.

Because stability testing is so expensive, there are significant cost advantages to limiting the number of structures that are tested. One scientific approach determines the critical moisture level of the product and pinpoints the level of protection required. With this data, one can match product protection requirements to packaging material capabilities and can optimize structures so that only a minimum number need to undergo stability testing (3).

Material suppliers must be involved at this point in the process. Early vendor involvement not only provides valuable expertise in matching materials to barrier requirements, but also can bring data about new structures to the discussion and offer solutions for various issues such as compliance, child resistance (CR), and counterfeiting.

As the development of the package structure proceeds in preparation for stability testing, the marketing and manufacturing departments should be involved so that their requirements can be built into the design from the outset. This involvement also facilitates the decision of whether packaging will occur in house on existing equipment or on a new line or if it will be outsourced. Outsourcing is a common solution when pro-

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duction capacity or required equipment isn't available in house. Manufacturers should decide where packaging will occur early on before preparation of the new drug application (NDA) begins. An early decision is especially important if the new product will require the installation of a new line because lead time for equipment is usually at least a couple of months and can take a year or more when complex machines are involved.

Legal or regulatory personnel also should be involved early in the process to vet potential brand names and avoid problems with trademark registration down the road. Before the name is finally decided, it should be reviewed in conjunction with the names of products that are already on the market to ensure that it won't confuse caregivers. This drug name review is particularly important because many medication errors are attributed to confusingly similar drug names that result in prescribing or dispensing mistakes.

The structural development phase is also the time to consider whether the

Pharmaceutical products requiring CR packaging* 16 CFR, chapter II, section 1700.14

- Acetaminophen
 - Aspirin
 - Methyl salicylate
 - Controlled drugs
 - Prescription drugs
 - Iron-containing drugs
 - Dietary supplements containing iron
 - Diphenhydramine
 - Ibuprofen
 - Loperamide
 - Mouthwash
 - Lidocaine
 - Dibucaine
 - Naproxen
 - Ketoprofen
 - Fluoride-containing products
 - Minoxidil
 - OTC products with active ingredient formerly available only by prescription
- * Some categories stipulate an ingredient level and/or exemptions

product will benefit from compliance aids, counterfeiting protection, and other functional features such as unit-dose dispensing. Compliance aids such as printing blister lidstock with the days of the week or times of day of the dosage regimen can significantly improve compliance. Anti-counterfeiting measures protect not only the consumer, but also the brand. Regulatory requirements such as tamper evi-

dence (TE) or CR also should be considered at this point.

CR, or what the Consumer Product Safety Commission calls *special packaging*, is required for most prescription (Rx) drug products, certain over-the-counter (OTC) drugs such as acetaminophen and aspirin, OTCs with active ingredients formerly available only by prescription (so-called Rx-to-OTC switches), most

Packaging design checklist

- Assemble a team with representatives from relevant departments.
- Ascertain product–package compatibility
- Involve suppliers.
- Optimize material performance versus cost
- Perform stability testing.
- Build in functionality (dispensing, compliance aids).
- Meet regulatory requirements (labeling, CR, TE, etc.).
- Review manufacturability.
- Select the manufacturing site.
- Draft packaging portion of NDA.
- Design graphics.
- Maximize shelf impact.
- Consider recycling–environmental issues.
- Design secondary–tertiary packaging.
- Consider shipping–storage issues (e.g., temperature sensitivity).
- Optimize cube.
- Perform vibration and drop testing.

iron-containing products, and some mouthwashes. An overview of such requirements can be found at <http://www.cpsc.gov/businfo/regsumpppa.pdf>.

According to 21 *CFR*, Chapter I, Part 211.132, TE packaging is required for retail OTC drug products (except dermatologicals, dentifrices, insulin, and the lozenge dosage form). In addition, products in two-piece hard gelatin capsules must use sealed capsules. A TE package has one or more indicators or barriers to entry that, if breached or missing, can rea-

sonably be expected to provide visible evidence to consumers that tampering has occurred. The barrier or indicator should incorporate an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture) and also must be flagged on the package to tell consumers about the protective feature. This flag should provide a detailed description about the TE devices. Once the design for the primary package is finalized, stability testing begins.

Secondary packaging

With stability testing underway, work begins on secondary packaging such as cartons and tertiary, or distribution, packaging (e.g. corrugated cases or insulated shippers). Considerations for secondary packaging include space for patient information, shelf impact, and cube, or how efficiently the cartons will use the space that is available on the retail shelf and inside the shipper. Cube remains important in the specification of distribution packaging, but attention also must be directed toward regulatory and manufacturing requirements, protection from distribution hazards, and cost.

Secondary packaging typically receives strong input from marketing. “There’s a lot of interaction [among marketing, research, packaging, manufacturing, and other groups] throughout the process,” notes a package design expert. The graphic designer generally enters the picture at this point. Although often completed in house, it is not uncommon for graphic design to be outsourced.

Interaction between various company departments is essential throughout the design process.

Once the manufacturer receives the stability test results and has decided where the product will be packaged, the packaging section of the NDA can be written. Guidance for writing the NDA can be found at <http://www.fda.gov/cder/guidance/1714fnl.htm>. Current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures are included in 21 *CFR* Parts 210 and 211.

Plans for testing finished packaging can be finalized at this point. Possibilities include vibration and drop testing to ensure safe passage through the distribution environment.

Meanwhile, packaging personnel work with members of the marketing, regulatory affairs, research, and labeling departments to finalize all of the components and write finished specifications. With the details finalized and the NDA filed, the product is ready to move into production and distribution as soon as FDA clears the NDA.

References

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