The Biofore Company UPM

WHITE PAPER

Migration safe pharmaceutical labels improve patient safety

UPM RAFLATAC

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Executive summary

Packaging is the first way consumers and healthcare workers interact with drug products: from their brand presentation and usage information, to their drug delivery mechanism and ongoing performance.

Meanwhile, packaging is how pharmaceutical manufacturers protect, present and identify their pharmaceutical and health care products.[1] The material choice will govern how a product is manufactured, sterilized, labeled, bundled, distributed and presented to end-users.[2] Increasingly, that material is plastic. While plastic is endlessly versatile, lending itself to myriad forms, it also faces increased scrutiny from regulators because of the material's greater potential risk for interacting with other components of the container closure system or the drug itself.

Labels play an invaluable role in identifying drugs and providing critical usage instructions. That's why label performance is so critical. Low-performance labels which create leachable chemical compounds may fail testing or perform poorly across the product lifecycle, resulting in significant launch delays or costly recalls.

This technical white paper is designed to empower decision makers at pharmaceutical packaging companies, converters, and global brand owners with:

- The pros and cons of using glass and plastic packaging forms for your pharmaceutical and health care products.
- Insights on how and why label materials leach into packaging forms, and why the wrong label products may actually cause significant business harm.
- Recommendations on how your label provider can help you streamline packaging testing and reduce the strain of taking new products or packaging forms to market.
- The importance of following the industry's best practices including change management procedures.

1 Pharmaceutical Packaging Market by Packaging Type, by Raw Material, by Drug Delivery Type by Region (North America, Europe, Asia-Pacific, RoW) – Forecasts to 2020, Research Report, page 32, http://www.marketsandmarkets.com/pdfdownload.asp?id=890&utm_source=referral&utm_medium=linkedin&utm_campaign=linkedin-pdf.

2 Ibid.

2. Drug packaging helps ensure patient safety

As the world's needs for pharmaceuticals grows, packaging companies stand ready to help drug manufacturers bring innovative treatments to market.

Numerous conditions are increasing the need for medicinal drugs, including an aging population and patients with intractable illness and chronic health conditions. Pharmaceutical companies are leading the way with innovative treatments for healthcare conditions that blend drug compounds and innovative delivery mechanisms to meet customers' needs. Small wonder that the overall global pharmaceutical market is slated to reach $1.3 trillion by 2018.[3] Packaging will play an important role, growing to $84 billion by 2020.[4]

In the brave new world of smart, precision medicines that lies ahead, pharmaceuticals will play an important role in giving patients more control and a higher quality of life.

Packaging is key to realizing this goal. Primary and secondary packaging work harmoniously together to secure and dispense drugs and provide vital information. Primary and secondary packaging that are both focused on patient safety form a container closure system.[5]

Pharmaceutical market is slated to reach **$1.3 trillion by 2018**

Since packaging forms are as various as the drugs they protect, this paper will focus instead on packaging material selection and how to ensure that final constructions achieve business, regulatory and patient safety goals.

> **From plastic bottles to blister packs, pharmaceutical packaging seals the deal: Packaging is a front line of defense, protecting medications from environmental or chemical exposure and helping ensure their effective usage and dispensing.**

3. Packaging, a multi-faceted performer

When patients hold a bottle of labeled medication in their hands, they may be aware of all the costly R&D behind the product. But chances are they don't understand the long and complex process pharmaceutical companies and their procurement teams have used to select packaging constructions and ensure that they meet tight regulatory and technical performance specifications. Let's look at the different types of packaging next.

3 "Global Pharma Sales to Reach $1.3 Trillion," Online Article, Thomson Reuters, August 4, 2015, http://thomsonreuters.com/en/articles/2015/global-pharma-sales-reach-above-1-trillion.html.

4 "Growing Use of Disposable Medical Products to Significantly Augment Market Growth of Pharmaceutical Packaging Until 2020, Says Technavio," Online Press Release, BusinessWire, February 25, 2016, http://www.businesswire.com/news/home/20160225005055/en/Growing-Disposable-Medical-Products-Significantly-Augment-Market.

5 "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, And Controls Documentation," US Food and Drug Administration, page 2, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070551.pdf.

3.1. Primary packaging

Primary packaging is the form that comes in direct contact with the drug product that is applied at the manufacturing plant and safeguards the product through its administration and usage. Pharmaceutical packaging is held to a much higher standard than packaging in other industries. It must enclose and protect the drug product, ensure its stability and performance, and guarantee its delivery. In addition, the packaging form must stay as stable as the drug itself: not changing or introducing toxic compounds, which could harm the drug and thus patient's health. Primary packaging includes all the components that come in contact with the drug including containers, closures, seals and more.[6] Labels can sometimes be a component of primary packaging.

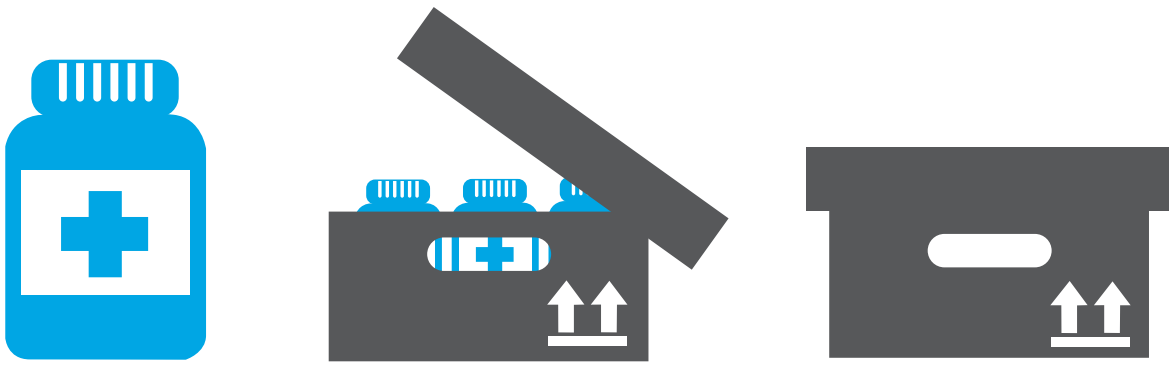
3.2. Secondary packaging

Secondary packaging includes packaging that doesn't have direct product contact, but is part of the overall construction and may provide added protection. Label constructions, including papers and films, inks and adhesives, are part of this construction.

Labels, as well as primary packaging provide product branding and usage instructions, including dosing and disposal instructions and the product's shelf-life, to encourage safe usage.[7]

3.3. Tertiary packaging

Tertiary packaging includes packaging used for logistics, such as boxes.



Primary packaging *Secondary packaging* *Tertiary packaging*

3.4. Packaging type matters

Why is this distinction so important? Brand owners will often spend considerable time designing fit-for-purpose primary packaging forms that meet all relevant requirements. However, secondary packaging decisions may be seen as a commoditized purchase. Decisions may come down to cost.

Let's look at why this approach may be short-sighted.

6 Ibid.

7 Dr. Simon Mills, "Pharmaceutical Packaging – an Overview Including Some Considerations for Paediatrics" Presentation, Training Workshop, 21 to 25 June 2010, World Health Organization, http://apps.who.int/prequal/trainingresources/pq_pres/workshop_China2010/english/22/003-PharmaceuticalPackaging.pdf.

4. The future of pharma packaging is plastics

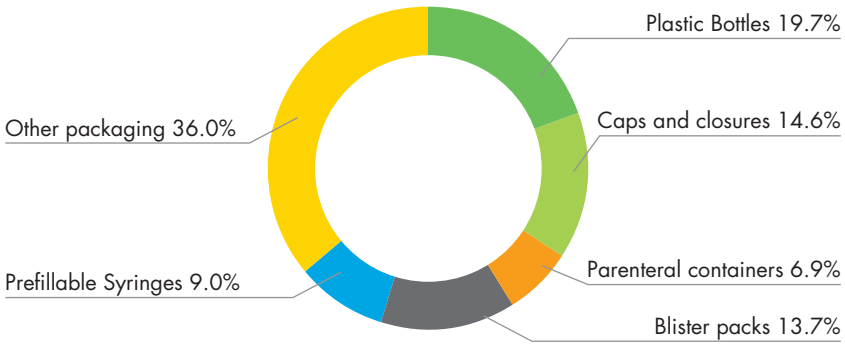
Pharmaceutical companies are increasingly choosing plastic over glass, and it's not hard to see why. Let's compare the pros and cons of these two materials:

Glass containers	Plastic (polymer) containers
Rigid material	Highly flexible material
Limited forms	Endless variety of forms
Risk breaking for vials and syringes	Are hard to break and don't shatter
Typically produced and stored until used	Can be produced as required
High weight	Low weight
Breakable	Rugged
Occupies fixed space	Can be collapsed for logistics
Can introduce glass particle contamination	Low risk for plastic contamination
Less risk of extractables and leachables	Higher risk of extractables and leachables

In addition, blow-fill-seal manufacturing of plastic containers is considered by many agencies to be a leading technique for ensuring aseptic, or sterile, processing.[8] Glass hole heads remain open for minutes, whereas polymer heads can be sealed between 0 and 7 seconds after exposure,[9] significantly reducing the risk of foreign particles exposure.

Plastic is used for nearly three out of every five pharmaceutical items

Plastic packaging represented nearly two-thirds of all packaging sales in 2015,[10] while plastic bottle sales alone constitute nearly 20% of the overall global pharmaceutical packaging market.[11]



8 "Blow Fill Seal," Online Entry, Wikipedia, Undated, https://en.wikipedia.org/wiki/Blow_fill_seal.
9 Michel Pittet, VP, Head of Pharmaceuticals Container & Delivery Syst., B.Braun Group, "IV Plastic Container Systems" Presentation, May 2–3, 2016. Not available online.
10 Global Pharmaceutical Packaging Market 2016–2020, Online Brief, December 2015, http://www.marketresearchhub.com/report/global-pharmaceutical-packaging-market-2016-2020-report.html.
11 Technavio Online Press Release, ibid.

However, using plastic packaging is not without its challenges. Here are some of the issues pharmaceutical companies should consider:

- Supply – Plastic material has an unstable raw material supply, and is experiencing pricing pressure in the European Union and Asia. Consolidation of key packaging companies may increase these pressures.
- Regulation – Plastic material is subject to higher requirements, such as extractable and leachable testing.
- Innovation – Healthcare systems are pushing manufacturers to increase patient safety, while the users themselves seek more convenience.[12]

5. Control and complexity: Navigating packaging development

Pharmaceutical packaging is heavily regulated. The agencies and governmental bodies overseeing this industry include the US Food and Drug Administration, Health Canada and European Medicines Agency, among many other groups. In addition, the Product Quality Research Institute (PQRI) Working Group has conducted research studies and issued best practices to help manufacturers of orally inhaled and nasal drug products meet regulatory guidelines for extractables and leachables. Due to their delivery systems, these products are among the most at risk for chemical contamination from their packaging.

According to Toxikon, all packaging must meet the following requirements:

- Be suitable for its exact intended use
- Protect the drug product it encloses
- Ensure that no toxic compounds are introduced into the drug product
- Be compatible with the drug product it protects
- Guarantee the drug product's performance and delivery[13]

12 Michel Pittet, VP, Head of Pharmaceuticals Container & Delivery Syst., B.Braun Group, "IV Plastic Container Systems" Presentation, May 2–3, 2016. Not available online.

13 Dr. Piet Christiaens, Toxicon Europe NV, "Extractable & Leachable Concepts for Containers" Presentation for PDA Workshop on Critical Issues in Modern Pharmaceutical Packaging, May 2–3, 2016. Not available online.

Plastic extractable and leaching risk grows with innovative packaging and delivery forms. This table depicts the drug products the US FDA states are at higher risk for packaging interaction:[14]

Drug package interactions			
Degree of Concern Associated with Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	• Inhalation Aerosols and Solutions • Injections and Injectable Suspensions 	• Sterile Powders • Powders for Injection • Inhalation Powders 	
High	• Ophthalmic Solutions and Suspensions • Transdermal Ointments and Patches • Nasal Aerosols and Sprays 		
Low	• Topical Solution and Suspensions • Topical and Lingual Aerosols • Oral Solutions and Suspensions 	• Topical Powders • Oral Powders 	• Oral Tablets • Oral (Hard and Soft Gelatin) Capsules 

5.1. Drug companies carefully control pharmaceutical packaging

Pharmaceutical packaging undergoes a long, complex and costly development cycle. As they review, qualify and manage their suppliers, companies:

1. Consider materials and forms against drug protection and performance needs.
2. Ensure desired packaging will meet patient safety, regulatory and business needs.
3. Develop authorization and qualification processes that provide complete transparency and documentation.
4. Create control and change management processes to meet tight specifications and manage any deviations.
5. Ensure packaging processes are audit-worthy and will pass all relevant authority inspections.

14 Container Closure Systems, ibid, page 6.

5.2. Switch from glass to plastic containers

If a drug company or a supplier changes a packaging form or material, such as moving from glass to plastic, internal teams and their partners will work through the tightly controlled change management process to make the switch. They must ensure regulatory compliance of new packaging before it hits the market and retail and hospital shelves.

5.2.1. Low-quality or incorrectly selected labels can pose extractable and leaching risks

Pharmaceutical companies obviously take care selecting labels. Labels must perform in a variety of usage conditions, maintaining adhesion and conveying product information. Regulatory and packaging development teams also know that inks and adhesives can migrate and affect packaging and drug products, which is why they are tested in conjunction with packaging.

5.2.2. Migration studies help increase drug safety

Before pharmaceutical companies can take drugs to market, they must perform migration studies on their packaging.

Most label constructions are properly tested and meet with success. However, occasionally they may not be properly validated or designed for their end-use. If the label construction fails, and inks and adhesives leach into drug compounds or the label interacts with the packaging or drug product, companies may face the following:

- Product launch delays – If pharmaceutical packaging fails testing, drug launches will be delayed. Since companies face enormous market and competitive pressures, this can mean the loss of significant revenue when a company needs to begin recouping R&D and development costs.
- Competitive advantage – Being first to market is often key for being the market leader for new products, "me too" drugs or generic offerings.
- Recall costs – Product recalls can significant sums in lost sales, logistics and destruction costs.
- Reputational harm – Pharmaceutical products that are seen as unsafe by consumers may take months or years to recover their former status in the marketplace.

Extractables

Compounds that result and can be extracted from a container closure system, when packaging encounters solvents in extreme conditions.

Leachables

Compounds that leak or migrate into a drug product from the container closure system under conditions that simulate those of intended use.[15]

15 David B. Lewis, Ph.D. Office of New Drug Quality Assessment, Center for Drug Evaluation and Research, US Food and Drug Administration, "Current FDA Perspective on Leachable Impurities in Parenteral and Ophthalmic Drug Products" Presentation, AAPS Workshop on Pharmaceutical Stability – Scientific and Regulatory Considerations for Global Drug Development and Commercialization October 22-23, 2011, page 2, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM301045.pdf also Committee for Medicinal Products for Human Use (CHMP) Committee For Medicinal Products For Veterinary Use (CVMP), "Guideline on Plastic Immediate Packaging Materials" European Medicines Agency Inspections, May 19, 2005, page 4, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003448.pdf.

> **In 2015, Sun Pharma had to recall 216,000 bottles of two medications, because the label varnish was leaching benzophenone into the drugs.[16]**

It's not surprising that the guidelines of the European Medicines Agency hold drug products at a higher risk for interaction to a higher standard. Inhalation, parenteral and ophthalmic products that are delivered in a non-solid dosage form and are not described in the European Union or a member's state pharmacopoeia, require extraction and interaction studies, as well as toxicological information.[17]

6. Test and test again

With so much at risk, the pharmaceutical industry is about command and control. Every time any key factor in a drug's makeup or production process changes, a company must follow a tightly controlled process. And new extraction and leachable studies must be started when companies:

- Develop a new product and select its container closure system or register the new product
- Change any new material during any part of the manufacturing process that directly contact the drug products
- Make a change to the primary packaging material, formulation or process
- Experience material failures[18]

Performing these tests can be a resource- and time-intensive process. As a consequence, pharmaceutical companies look for ways to streamline packaging testing and validation, without compromising patient safety.

> **Toxikon estimates that the cost for extractable and leachable studies for an inhalation product can cost $2.0 million and take 1.5 years.[19]**

16 Eric Palmer, "Sun Pharma Recalls More Than 216,000 Bottles After Label Leaches Chemical," Online Article, FiercePharma, September 24, 2015, http://www.fiercepharma.com/supply-chain/sun-pharma-recalls-more-than-216-000-bottles-after-label-leaches-chemical.

17 CHMP and CVMP Guideline, ibid, pages 10–11, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003448.pdf.

18 Dr. Alda Laschi, Analytical Expert, Corporate Quality, SANOFI PASTEUR, "Contact materials compatibility with biologics: Strategy and case studies" Presentation, PIRA's Extractables and Leachables conference, Rome, Italy, December 7–8, 2011. Not available online.

19 Michael Ruberto President Material Needs Consulting, LLC, and John Iannone Program Manager, Toxikon Corporation, "Extractables & Leachables Training," undated, http://www.toxikon.com/userfiles/files/PepTalk%20Joint%20Presentation.pdf.

7. Seek help from skilled and reliable packaging partners

Pharmaceutical testing is an important part of the industry, but there is no reason for pharmaceutical companies to carry the entire load. Packaging partners can help reduce the pain and strain of taking new products to market or changing packaging materials and forms. Here's how UPM Raflatac partners with its pharmaceutical customers to drive change through the supply change.

7.1. Industry best practices

UPM Raflatac follows industry best practices from groups such as:

International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)

Requirements for Materials Used in Orally Inhaled and Nasal Drug Products:

- Minimum 36 months of rolling availability of unchanged materials including:
  - Minimum 12 months of notice period to qualify a new material according to regulatory requirements.
  - Information on the shelf-life of the material
  - Last-call option to allow bulk purchases before production discontinuation
- Food additive compliance
- DMF (USA) number
- Heavy-metals tested
- Potential for materials/processes to produce foreign particulates should be as low as possible (contamination)
- Compliance with 1907/2006/EC (REACH)
- Information on composition, process and quality system
- Availability of controlled extraction studies data

Pharmaclear EUP gets the all-clear from leading regulatory expert

"UPM Raflatac's approach to follow industry's best practices including change management procedures is highly valued by regulatory experts", says **Juha-Pekka Nuutinen**, PHD, Director of Regulatory Affairs at Mectalent Medical Services. According to Dr. Nuutinen, the recent development of UPM Raflatac's Pharmacopoeia-compliant label stock product, clearly demonstrates UPM Raflatac's competence to meet industry requirements.

We also provide best practice guidance from all relevant industry groups, including:

- Polymer Forum
- The Extractables and Leachables Safety Information Exchange (ELSIE)
- Parental Drug Association (PDA)
- Product Quality Research Institute (PQRI)

7.2. Change management

UPM Raflatac supports pharmaceutical change management processes. We offer an established supply network, worldwide presence and long-term material supply, that meets IPAC-RS standards as described above.

7.3. Expertise

We offer industry and technical expertise pharmaceutical and packaging companies can leverage, including:

- A deep knowledge of legislative requirements and how they are changing
- Documentation on how our products perform on different materials and packaging forms
- Expertise with managing post-approval packaging changes

7.4. Two-way information sharing

We are committed to information sharing to reduce risks, while maintaining the confidentiality of our customers' business processes and information.

7.5. Pharmaclear EUP is a versatile performer

UPM Raflatac's Pharmaclear EUP film face stock combines a Pharmacopoeia-compliant label face with the RP31 Purus low-leachables adhesive. This label construction is ideal for labeling non-solid drugs in plastic containers and small-diameter containers. Usable for a wide range of applications, Pharmaclear EUP with RP31 Purus can help pharmaceutical companies streamline testing and reduce overall regulatory compliance costs, while protecting patient safety.

8. Conclusion

The pharmaceutical industry requires intensive cooperation among all participants, including drug manufacturers, packaging providers and label suppliers. By providing performance-guaranteed label constructions, label suppliers can help pharmaceutical companies achieve their business goals of ensuring successful product launches and reintroductions and implementing new packaging forms and innovations successfully.

Companies should use high-quality label constructions that are demonstrated to meet low-leachability and extraction requirements. Label partners can serve as key collaborators in providing exceptional drug products that help patients manage their health conditions safely and effectively.

UPM Raflatac in brief

UPM Raflatac is one of the world's leading producers of self-adhesive label materials. We supply high-quality paper and film label stock for consumer product and industrial labelling through a global network of factories, distribution terminals and sales offices. We employ around 2,900 people and made sales of EUR 1.4 billion (USD 1.5 billion) in 2015. UPM Raflatac is part of UPM – The Biofore Company. Find out more at **www.upmraflatac.com.**

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