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Microscopy, Microbiology and Regulations of Paper and Paperboard Utilized in Pharmaceutical Packaging

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The categories of pharmaceutical packaging are primary, secondary and tertiary containers. Primary packaging is in direct contact with the product. It provides protection from environment hazards (e.g., light, moisture, microbial contamination) during storage and handling without interacting with the drug (e.g., imparting odor or taste). For solid dosage forms, primary containers are glass, plastic, and blister packs. Secondary containers enclose one or more of the primary containers; they have no direct contact with the product. They serve several purposes, including additional protection during storage and handling, carry required labelling, and marketing purposes. Tertiary containers are for bulk storage, handling and shipping.

Paper and board are commonly used for secondary and tertiary containers. They are also used in the lidding material of some "peel off-push through" blister packs. The type of furnish and chemicals used in the papermaking process for each type of container is dependent upon characteristics needed in the final packaging container.

One widely used paper/board for secondary containers is made of virgin fibers that have been pulped via the kraft (sulfate) process and bleached by various chemicals (e.g., chlorine dioxide, hydrogen peroxide). Another popular board for secondary containers is made of kraft-processed unbleached virgin fiber. As interest in environmental sustainability has increased through the years, the use of 100% recycled fiber has also increased. The bleaching process removes color, making the final paper/board "white" in color while unbleached virgin paper/board is brown and recycled board is typically gray (Fig. 1). For pharmaceutical packaging, all of these are coated on one side with a high quality kaolin-based coating color to enhance printability. The boards are designed to have strength (rigidity), wear resistance, low moisture (water) adsorption, and be easily converted (e.g., fold, seal). Paper used for lidding material is made from bleached virgin fibers. The lid is a laminate of paper, polyester, and foil. The paper is clay-coated to enhance printability. One important characteristic of this paper is to have the appropriate elasticity (tensile) requirements for the conversion process. Common tertiary containers are corrugated boxes made from unbleached virgin, unbleached recycled fibers, or a combination of both. Strength properties of these boxes come from the design of a fluted sheet (corrugating medium) sandwiched between two flat sheets (liner). Corrugated boxes must be able to withstand stacking and various environments (e.g., high humidity) during storage and shipping.

No matter the type of furnish, the paper or board-making process is not aseptic. Of the different furnishes, virgin (bleached or unbleached) typically has low microbial contamination rates as compared with recycled. However, process factors, such as long-term storage without sufficient agitation, can lead to anaerobic conditions that allow anaerobic bacteria to flourish. If left unchecked, some anaerobes produce odors, such as volatile fatty acids. These odors recirculate throughout the process. They are also fiber-substantive, imparting odors to the final paper/board. Improperly treated influent water adds to the overall contamination rate of the process. Organisms, such as fungi (Fig. 2a), filamentous bacteria

(Fig. 2b) and encapsulated bacteria (Fig. 2c) can readily form deposits, especially on the machines. This leads to holes and other defects as well as breaks (e.g., production downtime).

Biocides are used throughout the process to minimize microbial growth. In the Unites States, all biocides are considered pesticides and thus are regulated under the Federal Insecticide, Fungicide, and Rodenticide Act and registered with the Environmental Protection Agency. Most biocidal actives are also "FDA-approved". This general statement refers to specific Code of Federal Regulations (CFR), 21 CFR § 176 (2014): Indirect Food Additives: Paper and Paperboard Components. The strictest allowance is 21 CFR § 176.170, components of paper and paperboard in contact with aqueous and fatty foods; 21 CFR § 176.180 is for components of paper and paperboard in contact with dry food. Section 21 CFR § 176.300 relates to actives used in the wet-end of the process. Although many mills do not produce food-contact paper or board, they still require all of their chemicals to have FDA-approval. There is no specific FDA regulation regarding the use of biocides for paper or board made for pharmaceutical packaging, thus the producers follow the 21 CFR § 176 guidelines.

Paper will continue to play an important role in the future of pharmaceutical packaging. In addition to being an integral component of various containers, uncoated and coated paper can offer solutions for tamper evident and security labels.

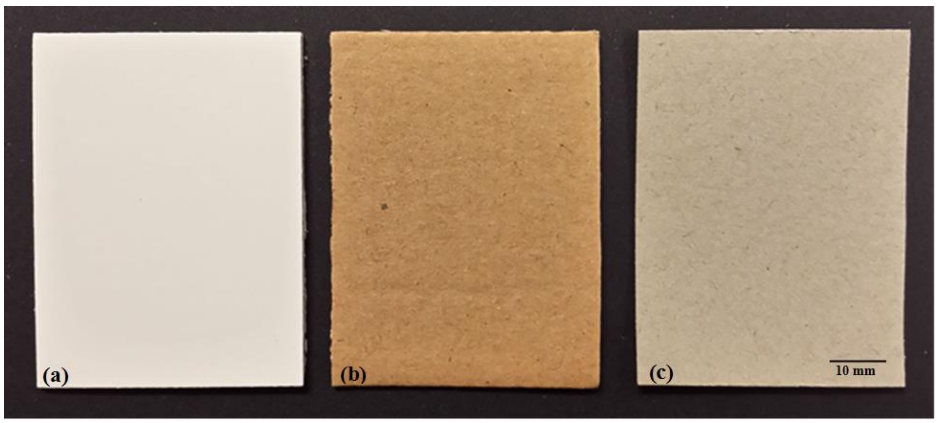

Figure 1. Paper/board made from various furnishes: (a) bleached virgin fiber; (b) unbleached virgin fiber; and (c) recycled fiber.

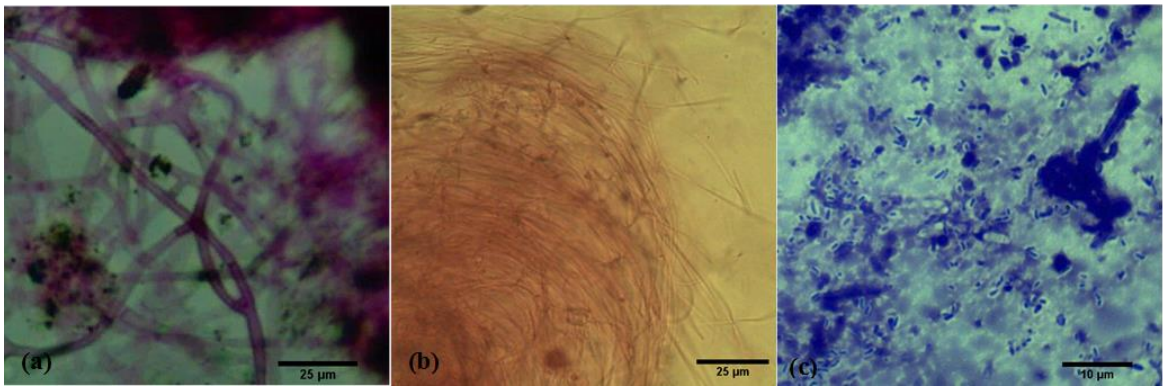

Figure 2. Problem-causing organisms in the papermaking process: (a) fungi - lactofuchsin stain; (b) filamentous bacteria – lactofuchsin stain; and (c) encapsulated bacteria – crystal violet stain.