

NAVIGATING THE REGULATORY LANDSCAPE:

SYNTHETIC SQUALANE CASE STUDY



Context

Squalane -- a cosmetic ingredient that functions as an emollient in lotions and moisturizers -- has been used as a softener for more than 25 years, according to the Personal Care Council's Cosmetic Ingredient Review (CIR).¹ Squalane is the saturated branched chain hydrocarbon form of squalene. The CIR indicates squalene is a triterpene polyunsaturated aliphatic hydrocarbon that is naturally occurring in large quantities in shark liver oil and other fish oils and in smaller amounts in plants (*i.e.*, olive oil, wheat germ oil, rice bran oil, palm oil). Squalene also exists in humans as a

component of sebum, an oily fluid produced by the sebaceous glands.

As shark liver oil contains the greatest yield potential for squalene, the manufacturing process to produce squalane often involves molecular distillation of shark liver oil and hydrogenation of the distillate, followed by a re-distillation step to produce a purity of about 96 percent squalane. The use of shark liver oil is controversial as some species of shark are listed as endangered and/or threatened by the U.S. Fish and Wildlife Service.² Manufacturing squalane using plant sources is an alternative option. Indications are the squalene concentrations



are much lower in plant sources and costs can be prohibitive for cosmetic formulators.

Description of the new technology

As reported in the New York Times on May 30, 2014, a synthetic biology version of squalane, manufactured by biotechnology firm Amyris, is commercially available for use as a cosmetic ingredient.³ Amyris, according to its website, uses “synthetic biology to produce target molecules.”⁴ Based on public information, the production appears to involve proprietary yeast strains that convert sugar to produce various hydrocarbons of interest, in this case, squalane.

Discussion of the legal and procedural issues

FDA regulates cosmetics and other substances under the FFDCa. Under FFDCa, cosmetics are defined to include “(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles.”⁵ Soap, as defined by FFDCa, is excluded from the definition of a cosmetic because of compositional distinctions and intended uses and is regulated separately by the Consumer Product Safety Commission.⁶ FDA regulates cosmetics in commerce under its FFDCa authority in conjunction with the Fair Packaging and Labeling Act (FPLA) as administered by the Federal Trade Commission (FTC). **Cosmetic ingredients and finished cosmetics, with the exception of color additives, do not require FDA approval prior to use in commerce. There are specific ingredients that are prohibited for use in cosmetics⁷ and FDA considers any ingredient**

that can impart a therapeutic response or affect the structure or function of the body to be a drug, not a cosmetic.

For squalane, the intended use as an emollient in lotions and moisturizers would be considered within FDA’s jurisdiction as a cosmetic ingredient, provided the intended use does not violate the fundamental concepts described above (e.g., does not imply a therapeutic or drug use), and it otherwise **comports with the basic principles of adulteration and misbranding as defined in FFDCa Sections 402 and 301**. Cosmetic manufacturers are expected, but not required, to comply with the FDA general principles of Good Manufacturing Practices (GMP). FDA has developed a draft guidance document⁸ for the GMP process that provides non-binding recommendations for companies intending to manufacture cosmetics in compliance with GMPs. Under the general misbranding and adulteration provisions of the FFDCa, however, FDA has the authority to pursue enforcement actions against cosmetic products that are not compliant with the law or regulations. The burden of safety and demonstration of intended use fall squarely on the cosmetic industry.

Finished cosmetics are required to be labeled correctly in accordance with FDA and FPLA statutes and regulations. Cosmetic claims on the product label, in promotional literature, advertising, trade press, and packaging are critical in assessing compliance with technical regulatory provisions and in determining a product’s intended use. The requirements are set forth in 21 C.F.R. Parts 701 and 740. The requirements for the declaration of ingredients are found in 21 C.F.R. § 701.3. FDA states that the ingredients must be identified in one of the following ways: by being specifically mentioned in 21 C.F.R. §

701.30; as defined by the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), the United States Pharmacopeia (USP), National Formulary, Food Chemicals Codex, U.S. Adopted Names (USAN), and USP dictionary of drug names; or in absence of being specifically listed, through the use of a name that is generally recognized by consumers or a chemical or other technical name.⁹ In this case, the labeling declaration requirements on the finished cosmetic could raise an issue of proper identification with respect to the synthetic biology squalane because there is no recognized or accepted standard to identify and distinguish squalane produced through synthetic biology.

The legal and regulatory takeaway

A key issue is whether squalane produced using synthetic biology and generated from engineered yeast rather than derived from known historical sources (such as shark or olive oil) is considered the same ingredient for regulatory purposes as those currently in commercial use in marketed cosmetic products. Or, conversely, is the synthetic biology version something different and more appropriately described using a descriptive generic name? The compliance issue for the cosmetic industry and FDA could be one of interpretation of FDA's current labeling and enforcement requirements: Is an ingredient derived from synthetic biology but labeled in the same manner as a substance usually extracted from conventional sources misbranded as defined in Section 301?

An even more consequential issue for the private sector is that FDA's authority in the area of cosmetics and cosmetic ingredients is more limited than in other areas, such as for drugs or biologics. FDA currently lacks authority to require pre-market approval for cosmetic ingredients (except for color

additives). Moreover, FDA's approach for oversight tends to be reactive rather than proactive for this category of product. In short, cosmetics -- whether produced conventionally or through synthetic biology techniques -- are not subject to regulatory risk assessment prior to market entry, yet the products are distributed and used by consumers, arguably the most vulnerable and least aware of the consequences of exposure and misuse. The regulatory burden remains solely with the cosmetic industry to demonstrate cosmetic and cosmetic ingredients are safe and do not impart any poisonous or deleterious substances that could result in injury to the health of the user, or consist, in whole or in part, of filthy, putrid, or decomposed substances.

FDA regulates cosmetic ingredients, whether conventional or from synthetic biology, primarily through a process that allows FDA to take action after a product is on the market if there is evidence that it is causing harm to humans or animals. Guidance for industry on FDA's "current thinking" about how cosmetics can be manufactured in accordance with GMPs is available, but compliance is not mandatory.

The key regulatory tools available to FDA to regulate risk from cosmetic products are enforcing ingredient labeling and product claims. Currently, products that include ingredients like squalane derived from synthetic biology use conventional labeling and nomenclature to identify them. FDA has not yet addressed whether cosmetic ingredients from synthetic biology are sufficiently the same as those from conventional sources to allow use of the same nomenclature.

The claims used to describe the attributes of ingredients produced from synthetic biology

may also present a novel enforcement issue for FDA and industry. It is unclear, for example, whether it is appropriate and non-misleading under FDA and the FTC's regulations to claim an ingredient is "natural" if it is the product of genetic manipulation of a non-conventional source. Similarly, it is unclear whether identification of the squalane source included in the ingredient label renders the product misbranded for failure to comply with FDA cosmetic labeling regulations.

As the cosmetic industry expands its use of synthetic biology in formulating ingredients and products, it is essential carefully to monitor enforcement trends and policy statements from both FDA and FTC. As these agencies grapple with the implications of synthetic biology in the context of their current, limited and somewhat outdated regulatory structures, it would be prudent for industry to exercise judicious scrutiny of ingredient labeling and proposed claims for cosmetic products to avoid any potential interpretation that would describe a therapeutic intention (potentially rendering the product an unapproved new drug) or fall beyond the scope of required labeling (potentially misbranding the entire product).

Endnotes

- 1 Cosmetic Ingredient Review accessed at <http://www.cir-safety.org/ingredients>.
- 2 U.S. Fish and Wildlife Service's endangered and threatened species list is accessible at <http://ecos.fws.gov/speciesProfile/profile/speciesProfile?spcode=E0CL>.
- 3 Stephanie Strom, *Companies Quietly Apply Biofuel Tools to Household Products*, *The N.Y. Times*, May 30, 2014, accessed at http://www.nytimes.com/2014/05/31/business/biofuel-tools-applied-to-household-soaps.html?_r=0.
- 4 Amyris, accessed at <https://amyris.com/innovation/industrial-production/>.
- 5 FFDC § 201(i), 21 U.S.C. § 321(i).
- 6 FDA, *Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)*, available at <http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm#Definecosmetic>.
- 7 For example, bithional, chlorofluorocarbon propellants, methylene chloride, and vinyl chloride, among others, are prohibited for use as cosmetic ingredients. See 21 C.F.R. §§ 700.11-700.35.
- 8 FDA, *Draft Guidance for Industry: Cosmetic Good Manufacturing Practices* (Feb. 12, 1997; revised Apr. 24, 2008, and June 2013), available at <http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm353046.htm>.
- 9 FDA, *Summary of Labeling Requirements*, available at <http://www.fda.gov/Cosmetics/Labeling/Regulations/ucm126438.htm>.



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