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NEWSLETTER

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In this Edition :

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FDA requirements for Cosmetics Manufacturers - by end December

By Steve Biddulph
Fellow of Royal Society of Biology. Board level pharma experience. QSM and Aseptic Manufacturing & Control Expertise

As we advised in our September 2023 edition, new FDA guidelines are now coming into force for cosmetic manufacturers of products on the US market.

Facilities and products must be registered by 29th December 2023

The Modernization of Cosmetics Regulation Act of 2022 (MoCRA) will help ensure the safety of cosmetic products. The FDA now require cosmetics manufacturers to register both facilities and products. Extracts from FDA guidance are provided below (Guidance for Industry: Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing) -

- Manufacturers and processors must register their facilities with FDA and renew their registration every two years. Equally, any changes to facilities must be updated with FDA within 60 days of the changes. FDA has the authority to suspend a facility's registration if the agency determines that a cosmetic product manufactured or processed by the registered facility and distributed in the United States has a reasonable probability of causing serious adverse health consequences or death to humans, and the agency has a reasonable belief that other products manufactured or processed by the facility may be similarly affected because of a failure that cannot be isolated to a product or products, or is sufficiently pervasive to raise concerns about other products manufactured in the facility. If a facility's registration is suspended, it is a prohibited act to distribute or sell (or otherwise introduce or deliver into commerce) in the United States cosmetic products from the facility.

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Responsible person Product listing

A responsible person must list each marketed cosmetic product with FDA, including product ingredients, and provide any updates annually. Responsible person means the manufacturer, packer, or distributor of a cosmetic product whose name appears on the label of such cosmetic product in accordance with section 609(a) of the FD&C Act or section 4(a) of the Fair Packaging and Labeling Act.

PAdverse Event Reporting

FDA has defined requirements for companies to record and report adverse events associated with cosmetics:

- A Responsible Person (RP) MUST submit any report received of a serious adverse event to FDA no later than 15 business days after RP receives it
- RP must keep records related to each adverse event report for their cosmetic product for 6 years (3 years for small businesses)

The FDA will enforce the above Regulations from 01.07.2024, and by December 29, 2024 a cosmetic product label must include contact information that consumer can use to report adverse events to company

nitrosamines –keep them out of your pharma products

By Jose Zapata
Galenisys Pharma Senior Expert. Pharmacist with frontline experience in Quality, Operations & Project Management.
PDD Certified

Nitrosamines are considered to be strong carcinogens that may produce cancer in diverse organs and tissues including lung, brain, liver, kidney, bladder, stomach, esophagus, and nasal sinus.

They can be **found in processed foods** as unintentional by-products of preparation and processing. Nitrosamines are formed by a reaction between nitrates or nitrites and certain amines. They and/or their precursors can be found in various products – including processed meats, alcoholic beverages, cosmetics & cigarette smoke. Vitamin C is known to inhibit nitrosamine formation, and manufacturers of cured meat are now required to add vitamin C to their products.

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Nitrosamines can be formed under acidic pH in the mouth or stomach, from precursors such as nitrite or nitrates - added to food or naturally occurring - **which may combine with amines to form nitrosamines.**

The pharma industry must also act to minimise these risks in formulations, processes, or blister packing.

The EMA published the first regulations on this subject in 2004(Regulation (EC) No 726/2004). relating to **chemically synthesised APIs.** They launched a call for review in September 2019 requesting MHA holders to review their manufacturing process is in order to identify and mitigate the risk of these impurities and report the outcome back to the authorities.

As well as with chemical APIs, there is also a risk of presence of nitrosamines in **biological medicinal products** with the following risk factors, according to the CHMP:

- Biologicals containing chemically synthesised fragments,
- Biologicals using processes where nitrosating reagents are deliberately added
- Certain primary packaging material, such as blister packs containing nitrocellulose.

I**n October 2023, EMA updated** the calculation for the "AI" (**Acceptable Intake**) of these substances in the ICH M7 (R2) guideline, (which defines N-nitrosamines as substances of the "cohort of concern" with limits in medicinal products).

We strongly recommend that all involved professionals should review this EMA update, including that in related ICH guidelines, to assure compliance in both "old" & "new" APIs, critical excipients, and in the compounds used for their manufacture.

In my audit experience at many pharmaceutical companies and suppliers, I generally found there is an awareness of the (old) nitrosamines risks. However, I noticed that the following points often need addressing:

- Risk management is not always or correctly implemented or updated.
- Some suppliers need to be approached for the additional new information required.
- The new acceptable intake limits have not been understood, or calculations made by manufacturers.

Galenisys experts can help companies to investigate this complex aspect of manufacturing, provide feedback & update precautions.

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Exploiting the Microbiome

By The Editor

Many years ago I went to see an old man from our village who was in hospital. The ulcer on his leg had never healed up. The wound had originally been caused by unruly child careering round with a supermarket trolley. On the door of his private room in hospital the nurse had written **MRSA**. He never recovered.

I was thinking about this a few days ago in the context of superbugs, another of which is **Clostridium difficile ("C Difficile")**. It too is resistant to traditional antibiotics. As a result the standard UK treatment for these infections is something completely different : **faecal microbiota transplantation ("FMT").**

Yes, this treatment is derived from human waste, which itself comes from **a vital part of the human microbiome**** that is to say the multitude of bacteria viruses and other microorganisms that live in our guts. These entities help breakdown our food, producing chemicals that regulate our bodies from within, including those repressing the growth of other harmful strains of bacteria.

With this knowledge the FMT treatment was developed. However, its manufacturing is a painstaking process which cannot be mechanised because the raw material is messy to collect, impossible to standardise, and hence supplies are way insufficient to treat all infected patients.

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So, researchers are looking for other ways of exploiting the potential of this part of the human microbiome, for example, by isolating individual species of bacteria and also investigating the metabolites that they produce.

As ammonia is linked to cirrhosis of the liver, bacteria which could metabolise the ammonia would be very useful. Also within the gut are bacteria killing viruses known as **phages** which can reduce the number of ammonia producing microbes. Trials are planned next year using such phages, for alcohol related hepatitis.

The biotech company Seres Therapeutics got FDA approval in April for a product which is the first oral microbiome therapeutic, and this is for use against the great enemy, recurrent C Difficile infections. Their drug SER-109 is made-up of diverse communities of bacteria which are delivered to where they normally act and could provide many possible beneficial effects simultaneously.

Seres are also testing SER -155, a mixture of 16 bacteria, in trials for leukaemia patients who have gone undergone stem cell transplants. This treatment also unfortunately requires large doses of antibiotics which severely damage the patient's gut microbiome, making them vulnerable to infections. Hopefully SER -155 will rejuvenate these severely damaged microbiomes. Other groups of immunocompromised patients could also benefit from this approach.

Meanwhile another biotech, Vedanta Biosciences, obtained good results in clinical trials on patients with recurrent infections of C difficile. The company has a fast-track approval from the FDA for a larger trial soon.

There is no doubt that exploitation of the human microbiome represents great potential, and a new era of medical research.

** See Galenisys September October Newsletters

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The FDA Acts against US manufacturers

By Steve Biddulph
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Articles in our past editions have both stressed the need for monitoring potential **bacterial contamination** in sterile products including **eye drops**; and about the mislabelling of **cosmetic and dietary products**.
This month November the FDA has acted against two companies faulted for these problems.

Recalls

Samples of lubricating eye drops from pharmacies in the USA have been found to be contaminated with several species of bacteria, including Pseudomonas spp. Bacillus spp. and Mycobacterium.

Eye drops have been sampled from Rite Aid and other Pharmacies and the manufacturing facilities inspected. **Many facilities were judged to have unacceptable risks of contamination.** These included :Dr. Berne's and LightEyez facilities. **Both companies have issued product recalls** and FDA has asked medical professionals to report any cases of adverse events linked to the products

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Consent Decree – False Claims

A U.S. District Court in Utah has entered two consent decrees of permanent injunction against Evig LLC, of St. George Utah, and the company's CEO, Douglas Lex Howard, as well as Premium Production LLC, of St. George, Utah, and its Manager, Ryan Petersen.

Their "**Balance of Nature**" products are **marketed as dietary supplements**, but **claim that the products could be used to diagnose**, **cure, mitigate, treat, or prevent diseases such as cancer, heart disease, cirrhosis, diabetes, asthma, and COVID-19 !!**

The FDA has not approved Balance of Nature products for any use, & hence they are judged as **misbranded & unapproved new drugs.**

In addition, Evig LLC violated current good manufacturing practice (CGMP) requirements, which rendered its products adulterated dietary supplements. Evig distributes Balance of Nature dietary supplement products through Amazon, Walmart, and its own online store at w.balanceofnature.com.

Galenisys again stresses the need for companies to define and implement systems for Contamination Prevention and Control so that they can ensure that their products are contamination free and pose no health risks to users. Our expertise in these areas has helped many companies establish & maintain robust & compliant systems.

Equally, manufacturers have to be aware that any claims that their products may improve well-being, imply that their product will be classified as drugs.