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November 2023 | NUMBER 32

NEWSLETTER

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In this Edition :

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The FDA "Office of Regulatory Affairs" (ORA)

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

This is the first article on a new series in which I will explain, & comment on, the functions, roles, and responsibilities of the different bureaux in the FDA.

First up is the ORA, I've met many of their personnel over 40 years, when FDA GMP inspections are being organised.

As we know the FDA is charged with ensuring that drug products are safe and are in compliance with rigorous standards for quality, safety and effectiveness. There are several processes for ensuring this through the evaluation of product registration files and the on-site inspections of drug product manufacturing facilities. The agency uses risk-based approaches to identify foreign and domestic facilities for inspection.
ORA is the FDA Bureau that organises all inspections and allocates FDA investigators to each one.

An inspection is a careful, critical, official onsite examination of a facility to determine its compliance with federal law. Although inspections are critical to FDA oversight, they are a snapshot in time, which is why inspections are one part of a comprehensive approach to oversee the safety and quality of FDA-regulated products.
Believe you me, it's a great feeling when the inspection result is good; and it's well worth preparing for these important milestones.

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Products manufactured outside the U.S must meet the same standards as products made in the U.S.

The agency remains vigilant in addressing potential issues in the global supply chain, so that Americans can be confident in the safety and quality of their products no matter where they are manufactured.

Who the FDA inspects:

The Agency inspects manufacturers of FDA-regulated products to verify that they comply with relevant regulations, including:

- vaccine and drug manufacturers
- blood banks
- food processing facilities
- dairy and produce farms
- animal feed processors
- outsourcing facilities and compounding pharmacies
- tobacco manufacturers

The ORA also organises the FDA inspections of:

- facilities that conduct studies in people (clinical trials)
- laboratories that conduct studies in animals or microorganisms when these studies are used to apply for FDA approval of a medical product
- foreign manufacturing and processing sites for FDA-regulated products that are sold in the U.S.
- imported regulated products at the border

Obviously, facilities that manufacture products that carry a high risk, such as injectable products manufactured by aseptic techniques and large volume parenteral products, are prioritised for inspection, and are inspected at a higher frequency.

Requests to Galenisys for help prior inspections, are often from sites making such high risk products.

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Corrective and Preventative Action – Food for Thought

By The Editor

Here at **Galenisys** we include **Corrective and Preventative Action** as an important item on our audit checklist when working with clients. Where problems are identified, they are added to the list of "CAPAs".

The logic around this is well established:

- Firstly, a problem needs to be identified.
- Secondly the problem needs to be corrected,
- and thirdly, action must be taken to prevent it happening again.

The preventative action will often be by checks, tweaks to procedures, and personnel training.

Last month (October 2023) a leaflet dropped through many doors in the UK to announce **Cholesterol Awareness Month**. To my surprise the leaflet advised that, in over 250,000 appointments, more than 50% of the people were found to have high cholesterol (UK).

OK this is the first step - Identification. How is the Corrective and Preventative Action going to pan out?

- Will people taking responsibility and change their habits (diet, exercise)
- Will they start taking true medication, if prescribed.
- Will they grab a bottle of "dietary / nutritional supplements" during the next supermarket shop;
- Or will they continue as before?

Food affects the mind as well as the body. We know the enjoyment at Thanksgiving or Christmas of joining with family or friends over a hearty meal. The meat in the meal contains animal proteins and all the amino acids that the body may needs, including many it cannot make for itself. A couple of these are needed for the production, respectively of, dopamine a neurotransmitter that controls feelings of pleasure and reward, and of serotonin which helps regulate mood.

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Vegetables such as Brussels sprouts contain folate, a vitamin without which the brain cannot function correctly. Fortunately, cranberry sauce often figures in such meals since it's involved, inter alia, in converting dopamine to another neurotransmitter, the lack of which seems to be associated with depression.

Mental health disorders get a lot more publicity now (24/7 television) whether or not there is more depression than there used to be. (Mind you there's a lot more we're **told** about nowadays, that we **should** be depressed by!).

Obviously, the human brain is very complex, and it's already clear that food, or additional nutritional supplements affect the brain. For example, the route to the production of serotonin alone requires vitamin B6, calcium, phosphorus, and iron.

Given this complexity it's fair to say that nutritional science is understudied. Studies face real difficulties given that the randomised controlled trials (RCTs), as used to test new **drugs**, are hard to set up for experimental diets. Few volunteers would wish to be restricted to the same food over many years. And who would fund such studies in any case, given that food and their components can't be patented?

Nevertheless, nutritional psychiatry has become an emerging field. As more of the population become aware of the link between nutrition and health in detail, the **corrective action** adopted by many seems to be to reach for the pills in the supermarket.

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Even 5 years ago ,43% of Asians and 54% of north Americans were taking a nutritional supplement. The global market for these in 2021 was over $150 billion. However, in many countries the regulation of the supplement industry is either weak or non-existent.

There is little rigorous research on benefits or risks, and the absence of serious studies in the field of nutritional psychiatry has provided a lucrative market for companies willing to aggressively promote these supplements. (Check out the shelf space they are given).

Here's an example of the risks: Mrs X was admitted to a psychiatric hospital with severe psychosis. Polar disorder and other afflictions were in her family history. Coincidentally her father & a friend had developed a range of supplements claiming that these reduce anxiety and stress in pigs. Mrs X credited the supplements with her recovery; and, via social media the story spread, and the pills sold widely.

There were no trials proving efficacy or safety. The publicity led one schizophrenic to abandon his prescribed medication, and he subsequently murdered his father and seriously injured his mother.

The downside of this & other stories is that micronutrients to treat mental health conditions became regarded as pure quackery.

But here are some assorted summaries of the results of “single item studies”:

- Studies have shown that B12 shortages cause depression and poor memory.
- Low levels of vitamin D are associated with increased risks of dementia and stroke.
- A recent RCT found that high doses of B6 reduces anxiety
- Too much vitamin A can be harmful in pregnancy
- There are a variety of health risks from taking beta carotene and vitamin E
- A large RCT study (2000 people) estimated that's three years of supplements led to a 60% slowing of cognitive decline in over 65s.

So high doses of 1 nutrient can be beneficial in certain circumstances or can interfere with the action or absorption of other nutrients.

Finally, to add to the complexity of food & health considerations; and as discussed in the two previous additions of this newsletter, **“Actually we love bacteria”,** there are the intriguing discoveries of the importance of the microorganisms in our intestines which regulate what happens to the food in our diet and hence the results in our brains.

It’s all FOOD FOR THOUGHT and there’s a lot to digest - Bon appetite

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The FDA Office of Compliance

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In this, the second article in the new series, we'll look at the **Office of Compliance.**

The **Office of Compliance (OC)** mission has been expressed as follows ".....(it) shields patients from poor quality, unsafe, and ineffective drugs through compliance strategies and risk-based enforcement actions. OC makes strategic and risk-based decisions that are guided by law and science to foster global collaboration, promote voluntary compliance and takes decisive and swift actions to protect patients".

It must be remembered that after site inspections, as an example, it is OC who decide on the state of compliance, not the investigator who performed the inspection.

Here are various aspects of the OC's role:

- Address patient health risks that arise from violations of FDA regulations and law. Develop risk-based enforcement and communication strategies to reduce and prevent patient harm associated with these violations.
- Work to protect consumers from unsafe compounded drugs.
- Protect the integrity of the legitimate drug supply chain and minimize consumer exposure to dangerous products marketed outside the legitimate supply chain.
- Monitor the quality of human drugs through facility inspections, product testing, and other pre- and postmarket compliance activities.
- Ensure drugs in FDA approval system have reliable evidence of safety and effectiveness, human subjects in clinical trials are protected, and drugs meet post market safety requirements.
- Develop policies and compliance strategies to help ensure that over-the-counter and prescription drugs are properly labelled and meet drug approval requirements.
- Coordinate evaluation and classification of drug recalls, and work with FDA offices globally to implement recalls.
- Monitor and assist with alleviation of drug shortages involving compliance issues.
- Provide support and guidance on developing potential investigations and regulatory actions to FDA offices around the world.
- Maintain the electronic drug registration and listing database and work to ensure the information in the database is up to date and accurate.

PS In our last newsletter I advised readers that the FDA had introduced compulsory Registration of Cosmetic Products, their ingredients, facilities, & locations, by the end of 2023 for the US market.

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