

October 2023 | NUMBER 31

NEWSLETTER

In this Edition :



Actually, we love bacteria - part 2 (P2)

Bacteria are essential for us & can help solve the big future problems.
The Editor

Regulatory action against Cosmetic company (P6)

Steve Biddulph

As in the USA, Quality and Regulatory Compliance is becoming increasingly important.

The EMA Herbal Preparations Consultation is a "HEADS UP" (P8)

Jose Zapata

The Misuse and Mistrust of Pharma Products (P10)

The Editor



Actually, we love bacteria – part 2

Bacteria are essential for us & can help solve the big future problems.
The Editor

Our September Newsletter carried part 1 of “Actually, we love bacteria”, looking at how bacteria help animals, plants, & other bacteria. In this article we look at how they help humans.

Not just a holobiont, but also a Torus

I never thought of myself as a Torus, but you & I should be grateful that we are. Topologically a human being is a Torus, a three-dimensional object with a hole through the middle, which is the alimentary canal. Nearly the whole surface of this Torus is home to microbes, though different parts have different bugs.

Half of the cells in our body are “us”, the other half are these bacteria. By far the largest number of them live in the lower gut. “Homo sapiens is the best studied animal holobiont of all” which is good news.

For example these gut microbes extend the digestive capabilities of the human holobiont in the same way (though not to the same degree as with termites), by breaking up fibrous plant polymers into smaller molecules that “our” cells can metabolise.

But they produce lots of other molecules too. Some of these send signals to the holobiont animal cells (“us”). Moreover these cells often signal back. This signalling seems particularly influential over parts of the nervous system. Among the molecules secreted by gut bacteria are serotonin, GABA, and catecholamines. All 3 are neurotransmitters, chemicals which carry impulses between nerve cells. The microbiome is thus an integral part of the gut brain axis – highway of the constant neural chatter between the largest group of nerve cells in the body (the CNS) and the second largest (the enteric nervous system).

Continued on next page ...

A new meaning to “we are what we eat”.



The third big interaction between host and microbiome involves the immune system. This brokers the deal that keeps the whole show on the road by preventing any particular part of the microbiome running riot - a task at least as important as fending off infectious diseases. In return a well-balanced microbiome assists the immune system by preventing pathogenic bugs from multiplying in the intestines.

The gut microbiome is thus deeply integrated with the mammalian part of the human holobiont - as can be seen when that integration goes wrong. Dysbiosis, as this is known, is at least associated with, and in many cases probably helps cause obesity, diabetes, high blood pressure, atherosclerosis, asthma, inflammatory bowel disease, some liver diseases, various cancers, autism, Parkinson's disease, and depression, (not an exhaustive list!!)

The Vegans may have it right.

What else does “our other half” do? It’s found that a largely plant based diet encourages fibrolytic bugs in the gut, while a meat rich one favours those that thrive on fat and proteins. As a consequence, plant-based diets yield molecules such as butyric and propionic acids which are known to regulate inflammation and other immune system functions. Meat based ones result in branched chain fatty acids and phenols and indoles which have a range of bad effects, including being risk factors for cardiovascular health.

The knowledge gained from holobionic studies is helping design more targeted pharmaceuticals, as well as explaining the side effects of some existing ones.

Continued on next page ...



- The “holobionic fix” – indirect ways bacteria help, or could further help, human beings.

1 For Crop breeders

- Workers for Indigo, a company in Boston MA, identify rare crop survivors in farmers' fields, after events like droughts and infestations, and send these plants in for study. The assumption being that there is something special about them.
- Indigo 's educated guess was that survivors had a different “rhizosphere” (the mix of bacteria & fungi attached to, or even penetrating the plant's roots).
- Fast forward through R&D, to the resulting “rhizospheric bugs” now sold by Indigo to give:
 - drought- tolerance for cotton, maize, soyabeans & wheat
 - improved resistance to fungi in maize soybeans and wheat
 - guard against nematode attack
 - liberate phosphorus and potassium from the soil.
 - and fix atmospheric nitrogen.



Pivot bio of Berkeley CA is concentrating on nitrogen fixation also. Their researchers have gene edited two types of nitrogen fixing bacteria to continue to work even in already nitrogen rich soil. Planting these bugs with eg maize seedlings can reduce fertiliser use by 20%

Continued on next page ...



Dr Ane, a scientific adviser to Pivot, has two other nitrogen fixing ideas being followed up:

- In a symbiotic relationship, legumes (pulses) have special root nodules to house nitrogen fixing bacteria. How about providing such nodules to key cereal roots? Eg Rice.
- Secondly, consider the excellent example of the holobionic nature of unusual strains of maize and sorghum. They grow aerial roots which secrete a gel in which nitrogen fixing bacteria like to live. This gel then drips to the ground where the fixed nitrogen is absorbed by the plant's roots. Good deal! By cross breeding with commercial cultivars this trait has been transferred to experimental plants.

2 For cattle farmers:

The termite like digestive systems of cattle & livestock generate more than 100 million tonnes of methane p.a. about 6% of greenhouse gas emissions for which we are responsible.

Bugs in that system can be curbed by adding to cattle feed either a chemical, or a seaweed (A. taxiformis) This latter not only curbs methane output but also increases the conversion rate of feed into milk or meat.

3 For conservationists

Both forests and coral reefs are temperature sensitive and thus threatened by global warming.

Researchers at the University of Wisconsin Madison have been looking at soil microbes and seedlings from **forest areas** which are 5.8 degrees of latitude apart. "Northern" seedlings of various species grown in soil inoculated with "northern" bacteria grew faster than those in soil with "southern" bugs; & vice-versa. Whereas inoculating entire forests is not practical, they expect that treating nursery grown saplings intended for local reforestation projects should help as the climate migrates.

(Holobionic) **corals** have photosynthetic "protists" (any eukaryotic organism not an animal plant or fungus) in the cells of the coral animals responsible for secreting the limestone. If the protists get too hot, photosynthesis goes wrong, free radicals are produced and "bleaching occurs. If bleaching persists the corals die.

Attempts to provide coral resistance to higher temperatures include gene editing the animal part, & tweaking either the protists, or other bacteria present in this holobiont.

Such ecosystem engineering illustrates holobionic thinking at scale. Only future R&D and experience will prove success or not, "but the very fact that it is happening at all is surely testament to an idea - holobiosis - whose hour has come".

References: Abridged & adapted from "What is an organism, anyway?" The Economist 17th June 2023

Nitrogen fixation, protists

Wikipedia

The Editor



October 2023 | NUMBER 31

Regulatory action against Cosmetic company



By Steve Biddulph

Fellow of Royal Institute of Microbiology. Board level pharma experience. QSM and Aseptic Manufacturing & Control Expertise

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.

The suspension of manufacture & sale of Joelle Ciocco products here in France was announced earlier this year by the “Agence National de Sécurité du Médicament” (ANSM) citing (CE) n°1223/2009.

The case of this French “high-end” cosmetics manufacturer Joelle Ciocco well illustrates the continuing need for the existing regulation, and enforcement, of these types of products in Europe.

Joelle Ciocco products contained the corticosteroid Betamethasone, despite it being banned in such products. Applied to the face it can cause thinning & flaking of the skin, acne, or depigmentation. Levels of other undesirable ingredients (two cyclopentasiloxanes) in excess of the limit authorised, were also found in certain products.

However, the misdemeanours of Joelle Ciocco don't end there. As well as illegal formulation, the company neglected (CE) n°1223/2009 Regulatory Compliance - the ANSM were not advised of the company formation, and it's exploitation of cosmetics; nor were the EU Commission notified of product launches on the EU market.

Additionally, notable by their absence were evaluation of product safety, and a formal procedure to ensure post marketing surveillance for adverse side effects. Mislabelling was also cited.



Continued on next page ...



However, other aspects of the company's business such as marketing & pricing had not been neglected. Effective publicity led to the company head being referred to as "the magician of the skin" or the "beauty guru of the stars"; and the pots of crème having "astronomical tariffs". The "Grand Soin", promising wonderful effects when cremes were personally applied by a sales assistant over 2hours in the Paris Institute of Beauty, was listed at euros 695, rising to euros 1350 when the lady herself was present.

Hard to know which would hurt most – the Acne or the Bill.

Fortunately, cases as bad as this are rare amongst European cosmetics manufacturers. Wise manufacturers continue to ask Galenisys to independently assess their Quality & Regulatory Compliance.

October 2023 | NUMBER 31

HERBAL PREPARATIONS - The EMA Consultation is a "HEADS UP"



By Jose Zapata

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

The European Medicines Agency, (EMA), via the Committee on Herbal Medicinal products (HMPC) published in July:

" A ..Reflection Paper on modern manufacturing techniques used for herbal preparations".

Which is out for consultation now, (deadline 15th November 2023). The document is of importance for plant extract manufacturers, as it already sees an evolution in manufacturing methodologies, & anticipates further developments. It believes that such new manufacturing techniques can **have advantages but also disadvantages.**

Here's a summary of the paper:

"The manufacturing of herbal preparations has always been considered close to traditional/conventional techniques, which involve the use of extraction solvents of different polarities such as ethanol-water mixtures for generally obtaining extracts for further processing. Only little information regarding the manufacturing processes is given in relevant monographs of the European Pharmacopeia (Ph. Eur.) and (only a) few key parameters describe classic solvent extracts in the product information.

However, the traditional methods do not necessarily cover all preparations which may be available on the market and (which are) in traditional or well-established medicinal use. Modern, improved and non-conventional manufacturing techniques may complement the existing traditional methodology and optimise processes."

"Modern techniques could present various advantages over the conventional approaches, such as higher extraction efficiency, reduction in the use of organic extraction solvents, the usage of non- hazardous solvents, a reduction in the extraction time and the consumption of less energy.....these methods may also have some disadvantages linked to various issues of technical reliability, consistency, homogeneity, stability, validation, qualification, documentation, transferability or scale up."

Continued on next page ...

"The emergence of modern manufacturing techniques **may impact the quality dossier content and assessment needs** for HMPs, including aspects of the correspondence/comparability of herbal preparations. Scientific discussions at HMPC on newly available data on supercritical CO₂-extracts indicate the need for guidance to be able to address herbal active substances not obtained with conventional solvent extraction in general and regarding comparability between preparations obtained by different manufacturing techniques.....dialogue is necessary to include innovation and application of modern technologies without any derogations to (the) established quality standards and conventions of Ph. Eur. and EU guidelines in order to ensure high and consistent quality of HMPs."

We can see in the above wording that the EMA is concerned that the new manufacturing techniques could have adverse Quality Assurance impacts. Further out, it's likely there will be regulatory scrutiny of testing, validation etc and an increasing need for the related documentation to be available in a QA system.

Herbal Medicine Manufacturers in the EU would be well advised to include all the related components of a robust QA system as they adopt or continue with novel manufacturing & testing techniques.

As always Galenisys experts will be available to assist in such compliance projects.

José Zapata



October 2023 | NUMBER 31

The Misuse and Mistrust of Pharma Products

By The Editor

A recent newscast carried a review of the approval of a new pharmaceutical product, and the type of patient it was designed to help. The spot ended with the throwaway line “.... of course, all pharmaceutical products have undesirable side effects”.

It strikes me as likely that this sort of comment reinforces the regrettable mistrust of medicine, as we have seen manifest by the “anti-vaccers”.

As so often it's vital to consider context. Mistrust has resulted from several factors.

Firstly, consider misuse, and the case of **Ozempic** which is a drug authorised for the treatment of type2 diabetes **only in patients where their illness is insufficiently controlled by other treatments**. Its active ingredient stimulates the needed insulin & glucagon.

But as it also reduces food intake by slowing stomach emptying, and reduces the appetite for fatty food, it is now being **misused** for slimming.

The product – in the form of an injectable solution in a blue pen – **trends on Tiktok** where celebratory influencers demonstrate their svelte forms thanks to their “secret friend”! The platform hosts thousands of endorsing videos which have attracted millions of views, principally by young female viewers susceptible of being impressed.



Continued on next page ...

However, the key thing is this. **Stopping its use leads to the user regaining the lost kilos, so misuse continues.** This continued misuse for weight loss can lead to side effects including serious ones – dehydration caused by gastric trouble affecting renal function, acute pancreatitis, and suspected cancers of the thyroid.

A more responsible (though sadly less followed) “influencer” is the French consumer magazine “**Que Choisir**”. It’s October edition headlines “LISTE NOIRE Ces médicaments à éviter” (“BLACK LIST These are the medicines to avoid”) and listing some 20 products whose use is unnecessary or which are used inappropriately; (as well as advising better alternatives).

Ozempic misuse is a repeat of the sad & much publicised case of **Mediator** (benfluorex), correctly prescribed for diabetes control, but misused such that it caused between 1500 – 2000 deaths. Despite such warning lessons the urge to slim persists not only amongst those grossly overweight, but also amongst those whose body mass index is in the normal range.

More generally there have been plenty of misuse alerts to inform the public of dangers, including those for Epitomax, Levothyrox, and the anti-depressant **Prozac**.

Other factors leading to mistrust are:

- Blatant & criminal promotion of products (eg Fentanyl; Captagon .), and mislabelling.
- Failure to read the instructions, or to follow doctor guidance.
- Use of multiple conflicting medicines concurrently, causing unforeseeable side effects.
- Continued use beyond the prescribed period, or dosage.
- The Product Inserts (leaflets) themselves. There are much longer inserts, listing more potential side effects (often insignificant), than decades ago. In part this is because post marketing surveillance is more fully implemented, communicated & enforced than in the past. And, given litigation, potential side effects are sometimes listed “just in case”.

We can only regret the damage all this does to the image of many valuable medications.

The Editor

