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NEWSLETTER

Tony Dunford Editor

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Exben Pharma & Chemical Benchmarking

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From lizards to clinical labs

By The Editor

Further progress in obesity treatment and avoiding its consequences.

As the GILA MONSTER only eats three to four times a year, one might reasonably deduce that this lizard can regulate its appetite, & doesn't suffer from food addiction. In fact, it has a very useful hormone in its venom called exendin-4. And in 1990 a researcher found that it was very similar to the human hormone Glucagon-Like Peptide 1, or “GLP-1”.

It's well known now that GLP-1increases the production of insulin*, the hormone that lowers blood sugar levels but that it is broken down very quickly after a few minutes. The lizard is better: its hormone stays active for hours. (* GLP-1 also appears to be a physiological regulator of appetite & food intake).

It took it took many years however before **Eli Lilly & Amylin Pharmaceuticals** developed and got approval for a **diabetes** product based on a “synthetic exendin-4” called Exenatide.

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The success of this alternative to injecting insulin encouraged much wider R&D. The boffins knew that GLP-1 also slowed the rate of gastric emptying, as the food stays longer in the stomach it obviously suppresses appetite. **Novo Nordisk** first followed this up and showed that their GLP-1 product could dramatically reduce body weight.

Now we've talked about obesity treatment in more than one Galenisys Newsletter. But the reason for us revisiting the subject once again is that there is a wider and wider range of possibilities being explored for these sorts of drugs; and there are important implications flowing from the understanding of their mechanism of action. This category of drugs and the further knowledge that related research is providing will be a major future feature of our industry.

The 3 approved products forobesity have become blockbusters, & the growing level of obesity worldwide ensures a lucrative and fast-growing market. Thus, numerous other companies have R&D programmes aimed at products to improve on Novo Nordisk and Eli Lilly's obesity brands.
Their objectives include tablets instead of injections, less frequent administration, preventing relapse, and avoiding side effects.

Replacing the guardrail

Zealand Pharma has followed up on the human hormone **amelin**, produced in the pancreas in response to food intake, which creates a feeling of fullness after a meal. Knowing that another hormone **leptin** usually indicates to the brain that the body is full **except in people suffering from obesity**, the company is researching analogues of amelin, which seem to make people sensitive to leptin again, and therefore will stop them eating so much. In phase one trials an analogue provided weight loss with less side effects.

The (positive) knock on effects

As obesity is linked to numerous health issues such as strokes, kidney problems, and liver disease; the GLP drugs are proving useful potential treatments for these conditions, or of their avoidance.

For example, last month the FDA approved the use of **Semaglutide** (the Novo Nordisk product already marketed for obesity) for **reducing heart disease risk** in obese / overweight patients. And the product also shows promise in reducing kidney events in type 2 diabetes patients.
Meanwhile Boehringer Ingelheim claim good trial results in treating a serious **liver condition** with their weight loss drug Survodutide.

Probing scientists are discovering more of the interactions between these drugs and the brain & immune systems, given that there are GLP-1 receptors in the human brain. The area of research has rich promise.
"MONSTERS" can be helpful.

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Corrective and Preventative Action

CAPAs and leveraging past experience.
By The Editor

Several decades ago, I took charge of a pharma manufacturing unit which filled and packed double ended ampoules. One department consisted of female operatives in a darkened room inspecting by hand filled ampoules in front of a light source, to eliminate those containing visible particles.

Quality Control were routinely rejecting some batches for high particle count. The first attempt at improvement was to introduce polarised light to increase detection in the inspection department. And this was successful, in as much as more rejects were found. (But “yields” went down).

Nevertheless, it represented “inspecting in quality” (widely accepted in the industry then, but of course not now). The introduction of polarised light represented limited **corrective action**, but not **preventative action**.

The next step was to try and identify the nature and source of the particles. Investigation quickly revealed that empty double ended apples ampoules arrived in plastic containers of approximately 200 packed in cardboard boxes. It took QC somewhat longer to find that most contaminating particles were cardboard fibres. A supplier visit followed, and it would it was agreed that henceforth the company would straight away place the plastic containers in clean sealed polythene bags before dispatch in cardboard outers.

It was pleasing to note that this dramatically reduced the number of particles in filled ampoules ie preventive action. The extra charge by the supplier was far outweighed by lower inspection costs and wasted filled ampoules, ie it increased yield.

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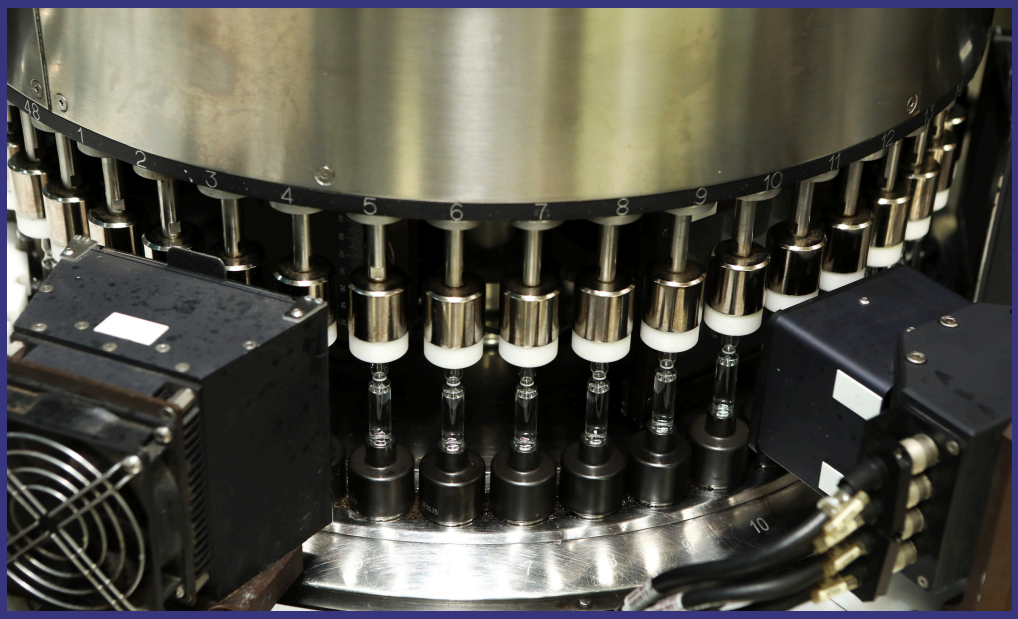

However, the cleanliness of the filling and packaging department still represented a problem. It processed ampoules & also filled and packed capsules into glass bottles. The factory layout necessitated bringing in wooden pallets and the cardboard outers used to ship products to our wholesalers, and the costs of disruption, area upgrade, & change to cleaner materials of construction were large.

Once again **preventive action** was to avoid particulate contamination in the first place. Within the group we had already started using laminate flow units over filling and packaging lines. The line was adapted to have vertical laminar flow above the bottle feed and filling station. There remained the problem of the incoming bottles. As always, it's imperative & beneficial to “visit”, ie audit, suppliers.

The purchasing and quality functions visited a new potential supplier in Italy and after discussions which confirmed commercial viability, we agreed with the supplier a contract under which he would install a laminar flow unit above the line immediately after glass moulding, and our quality function would train his personnel to identify and check for particles using our in-house test methods, and of course, pack in clean bags before the cardboard shipping outers, **ie 3 examples of leveraging our past experience.**
Many **corrective and preventative action** investigations can be more complicated, subtle, or political than these examples.

Over several decades Galenisys have accumulated considerable experience which is available to help clients establish and run such “CAPA” programmes.
These are a key tool for Contamination Control which Steve discusses in our next article.

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The FDA and Contamination Control

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

FDA, EMA and PDA are all increasingly focused on Contamination Control.

This, no doubt, follows the implementation of the new Eudralex Volume 4, Annex 1 requirements for sterile products, but FDA are pushing for a wider Contamination Control Strategy for all other product types.

The principles for a contamination control strategy remain the same as for sterile products, but it must not be forgotten that contamination may be caused by many things other than microbes:

- Fibres,
- non-viable particulates,
- degradation products,
- impurities,
- detergents,
- cleaning and disinfection agents, etc.

CLEAN??

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The staffing of the programme will require consideration of what expertise & experience is required and available, on site, or at or corporate level, and whether external support will be required.
These staffing issues can be more significant when new technology or products are involved, or incoming, via R&D or technology transfer.

Below I highlight some of the main principles & components to that a contamination prevention and control programme must contain.

The CONTEXT of the programme – sites . products, processes, sub contracting etc

PREVENTION as the essential approach - and this requires a risk assessment to understand the possible sources of contamination for stated products, processes & sites. Steps can then be taken to reduce the contamination at source, if this is possible.

Following the risk assessment comes the design and implementation of the TESTING regime, including realistic acceptance limits, and the absence of undesirable organisms,.

The ESTABLISHMENT of the programme including:

- Considering it as Project
- Training & Culture
- Funding needs
- Non-conformity identification, investigation and a CAPA system
- Programme “maintenance”, & integration with / leveraging of QA system elements

Galenisys have assisted many companies in defining & implementing Contamination Prevention and Control programmes; and also in the investigation & correction of contamination events.
For further information on our experience and services, simply contact us on
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Steve Biddulph

More about Less

Supply chain factors causing more medicine shortages, & especially UK post Brexit
By The Editor

The Galenisys Newsletter in March 2024 reported on the shortages of pharmaceutical products in the European Union & UK and how this problem was affecting patients. Now recent report from the Nuffield Trust throws further light on why this problem will persist, & effect the UK more than the US & EU.
The **Nuffield Trust** Report is backed up by comments from other sources in the UK supply chain. Drug shortages are a "new normal" in the UK and are being exacerbated by Brexit, the Report has warned.

SUPPLY PROBLEM WARNINGS UP 250% IN 3 YEARS

A dramatic recent spike in the number of drugs that are unavailable has created serious problems for doctors, pharmacists, the NHS and patients, it found. The number of warnings about impending supply problems for certain products that drug companies have issued has more than doubled from 648 in 2020 to 1,634 last year.

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Major shortages of products to treat ADHD, type 2 diabetes and epilepsy were common last year and some shortages still remain. “Some medicine shortages are so serious that they are imperilling the health and even lives of some patients…” the CEO of the National Pharmacy Association states “Pharmacists … are spending hours a day hunting down stocks,….”
Health charities for these illnesses have seen a sharp rise in calls from patients unable to obtain their usual medication.

GLOBAL PROBLEMS PLUS THE COST & HASSLE OF BREXIT

Global manufacturing problems linked to Covid, inflation, the war in Ukraine and global instability are major factors in the UK’s unprecedented inability to ensure patients can access drugs.

However, Britain’s departure from the EU in 2020 has significantly aggravated the problem the Report continued, pinpointing these specific problems:

- Some companies are removing the UK items from their supply chains.
- Leaving EU now results in the requirement for customs checks at the UK border,
- Quitting the EU’s European Medicines Agency, means UK now has to start approving drugs itself. The UK is now slower than the EU at making new drugs available.
- Post-Brexit red tape has prompted some firms to stop supplying to the UK altogether.

The Department of Health and Social Care has had to pay more to ensure continuity of supply, more frequently. These “Price concessions” (ie rises) rose from about 20 a month before 2016, to 199 a month in late 2022, and cost NHS England £220m in 2022-23.

As the EU’s 27 countries have recently decided to act together in price negotiations, this could leave British supplies even less of a priority for drug companies, in future. Pharma companies with new products to exploit will likely prioritise the far larger markets of the USA & EU in regulatory & commercial negotiations, to get to market.