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NEWSLETTER

Tony Dunford Editor

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RARING TO GO !!

The Editor

Refreshed I hope from a good holiday, seeing friends, exercise and a good book or two. And inspired by the outstanding performances at the Paris Olympics, I hope you're raring to go like we are.



So, ignore the / any bad news that inevitably will be talked up on the TV channels when the journalists get back from their holidays.

And look forward to some really interesting projects, which is just what we are doing

GALENISYS NEWS

The Editor

Galenisys is pleased to announce that it will be supporting one of the worlds most important biochemical manufacturers in the areas of regulatory and compendial compliance. The Galenisys marketing and client relations team have been working with this client for the last 6 months, so congratulations are in order!

A major American based pharmaceutical manufacturer has also contracted Galenisys for support in the area of technology transfer and sterility assurance.

Our Egyptian client has now submitted product registration documents to the local authorities and should soon be able to manufacture the first trial product batches. We are pleased to have supported him in reaching this key milestone.





WATER SYSTEMS - WATER FOR INJECTION?



By Steve Biddulph

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

(We're running a number of articles about contamination & avoidance. In this example Steve relates how one area of weakness jeopardises the whole site. Ed.)

WATER FOR INJECTION?

In a previous role as the Senior Director for Quality for the Americas, I evaluated many of our subcontract manufacturers. One particular CMO manufactured a series of parenteral products for us, mainly using aseptic techniques. I found that their facilities and equipment were modern, well designed and appropriately qualified. Personnel were well trained and well-grounded in aseptic techniques and behaviours. I eventually started to evaluate utility systems and once again found HVAC, compressed air, nitrogen, steam - industrial and pure - potable water and purified water to be well designed. These utilities were all qualified, validated, and well maintained and monitored.

In the Site Director's office, I said that all was well but that I hadn't had a chance to see the WFI system. The Director took off his white coat and put on his overcoat. It was a little early for lunch, but I did the same and followed him out to the street. We crossed the road and entered a block of flats and made our way to the top floor. The Director knocked on a door and a guy in slippers and bathrobe answered. « Can we see the WFI » asked the Director. The guy went away and came back with keys in hand. He opened a door at the end of the corridor, and we went up some stairs and out onto the roof. In front of us was a beautiful state of the art still.

When WFI was required, the still was switched on and water collected in aluminium milk churns that had been washed in potable water and then stored on the roof. Words failed me!

As I said in an earlier article « if you want to find issues, look at the water systems »

And if you've got a water issue already, or want to avoid having one, call Galenisys



MOVING FAST!!

The M pox virus certainly is.....and hopefully governments as well.
The Editor

Since we wrote about this outbreak in our August edition, the World Health Organisation has declared the Democratic Republic of Congo outbreak of a new variant of the M pox virus a “**public health emergency of international concern**”.

The WHO statement releases funds and assists vaccine availability. Other funds are coming from aid agencies & governments. However, there is no specific M pox vaccine at present, but existing vaccines against related pox viruses do provide some immunity, according to the WHO. Stocks of these are relatively limited compared with the quantity needed just for containment in Africa, and distribution to the affected areas is difficult.

The DRC has recently approved two mpox vaccines for emergency use and regionally-led efforts have started to secure doses and commence in an urgent bid to halt the spread of the outbreak.

CEPI is funding two studies of Bavarian Nordic's mpox vaccine (MVA-BN®) in Africa, as part of international scientific efforts on mpox vaccines. The first to study how well it works in children, and the second whether post-exposure vaccination reduces the risk of secondary cases or reduce severity of illness. CEPI is also supporting BioNTech's next-generation mRNA-based mpox vaccine, which is in early clinical development.

Of course, vaccines are “sticking plaster”. The main effort needed is by governments, by education and measures to ensure prevention & containment, as these are far less expensive than vaccines, protective clothing, and facilities for recovery.

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“Easier said than done” as the east of the DRC is a war zone with M23 guerrillas in control of large parts. The result is displaced persons camps, where it can easily be spread from Infected “sex workers” and those in the illegal mines. However, aid workers are battling on with some hopes of success given how well they did in containing Ebola in that same area.

A lot needs to be done. Since the outbreak started it spread to other parts of Africa & the Middle East.

Obligingly! the world's airlines are carrying it free of charge on international travellers to all continents. It's touched down in Europe already. Airfinity, a health data firm, report that Dubai and London are at the greatest risk of importing the new strain.



Lethality of the virus is thought to be in the range 1.4 to 10%, with children the most vulnerable, particularly if they are undernourished and thus have weakened immune systems. At least infected cases are readily recognisable, (unlike COVID), as M pox causes fever and pus-filled blisters on the skin.

All governments should have used the lessons from the COVID epidemic to put measures in place for surveillance, contact tracing and diagnosis. However, many haven't even had investigations into how well they performed. In the UK, the COVID public inquiry (whose start was postponed by Boris Johnson), released the first of 9 “modules” on the country’s readiness for pandemics only in July this year!

The next few months should show to what extent the lessons have been learned and acted on in various countries.



The Project Manager's Notebook: Part 2 of WHAT?

A continuing series of articles by our Team Member based on his global pharma project experience

In our August edition. I talked about the importance of defining the Scope, Process(es), Context, and Scale of the Project as key steps in getting to the total project cost for budget purposes.

With these factors defined we can use the concept of the “**Work Breakdown Structure**” to improve the cost estimates, by breaking the project down into **Equipment, Utilities and Service Packages**.

The **Package Costs** can now be defined by the respective engineering disciplines in the Package Scope or User Requirement Specification (“Cahier de Charge”). These engineering resources may be “in house” ie. part of the client's organisation; or outside consultants, or a mixture of both but need to be chosen with care *. (Rather than having perhaps 15 different engineering groups to manage, the client may prefer a resourced General Contractor to prepare packages or manage the groups).

At this stage the costs generated by the above activity will be prior to full Project Approval (note 1) and will give Management much more accurate total.

In preparing the equipment, utility and service packages, the following things need to be taken into consideration:

- 1.Package construction inevitably involves an element of design.
- 2.Project Design Review / Qualification needs to take place before packages are ordered (Note 1)
- 3.The packages need to take account of any architectural necessities or preferences.
- 4.A check to ensure there are no gaps or overlaps between the packages, and that they have compatible standards & software.
- 5.Validation needs to be considered, as the Validation Master Plan, should be drawn up based on knowledge and approval of the packages.
- 6.(To the total of package costs should be added an inflation % allowance; and a contingency allowance (often 10%)).

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*For example. A post project review of (an otherwise very successful) large project, identified a key area of weakness in the choice of the Building Management System (BMS) Supplier. A company of outside electrical and software consultants had been chosen to prepare the electrical & BMS packages.

This consultancy (who later signed off on supplier choice) had neither the experience of preparing a BMS package of the required complexity, nor of auditing suppliers for the required capability. Since commissioning / qualification of a BMS can only start when control instruments, cameras & software are in place the competence issues only surfaced near project completion.

Do check the various features of the packages, proposals, changes etc using the 8 soldiers: WHO, WHAT, WHEN, WHERE, WHY, ON WHAT CONDITION, HOW MUCH, HOW OFTEN.

Notes

1 Unless "Time is of the Essence" see a future article.

"Aubonne"

Galenisys can provide detailed advice on specific aspects of Pharma Project Management on request.



GENETIC SCRABBLE

**Did a board game inspire the scientists?
The Editor**

In Scrabble - a board game which can be played by all ages - people are dealt letters, and if they have the right letters, they place them on the board in the right order to make a correctly spelt word. (Long words in the right place win).

In life, people are dealt lots of letters in the famous “double helix”. But sometimes the letters are not in the right place to “spell” correctly, or a whole long “word” is just plain wrong.

This leads to genetic diseases. But happily, now, scientists have figured out how in principle to change the letters, and are getting better and better at doing it.

Maybe the scientists played Scrabble when they were young!



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CRISPR CAS 9 - only discovered in 2012 - is one technology which has moved from lab to clinic at lightning speed. To date, this **gene editing** technique has been used to improve the vision of people with an inherited condition causing blindness.

Using the technique Vertex and CRISPR Therapeutics co-developed CTX 001 (known today as Casgevy) as a one time treatment for curing rare sickle cell disease. But at a price of \$2.2 million!! This very well illustrates that these techniques & products face both economic and technical challenges. However there are reasonable hopes of using it to tackle cardiovascular disease and cancer, which, unfortunately, is a mass market.

The technique consists of cutting the DNA with the enzyme CAS 9 at the exact required spot in a single strand version of the DNA. As the body has natural repair cells, these get to work repairing the cut. But now gene editing medicines take control of the repair process so it ends up inserting the correct sequence, hopefully. In our Scrabble analogy, this is equivalent to throwing all the letters on your stick away, and (hopefully) replacing them with good ones out of the bag.

As in Scrabble, this strategy doesn't always work. In a CRISPR Cas9 procedure, the RNA guide molecule can sometimes lack precision ie cuts in the wrong place, or the repair process causes unintended insertions or deletions. A cancer could be an eventual result.

So, research efforts were for a new generation of more precise and efficient tools for gene editing: **CRISPR Cas9 nickases**, for example, are enzymes that cut only one strand of the DNA double Helix, so are used in pairs. There's little chance now of the same error twice.



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“If only I had a G”

Another method, “**base editing**”, can change a single letter of a DNA sequence into another without the need for cuts.

Verve Therapeutic’s product “Verve 101” turns off the PCSK9 gene in the liver by making a single letter change in the DNA (from A to G) in patients with “familial hypercholesterolaemia” (score 264 in Scrabble!). It affects one in 250 people who can only remove bad blood cholesterol with difficulty. This procedure has already been trialled in patients.

The approach of Beam Therapeutics, is to make 4 DNA letter changes to immune cells so they attack leukaemia better. They’re also developing also a product for the same diseases as Casgevy, and hope for improved results in late 2024 from current trials.

Even slicker approaches have been postulated and are now being tried. Including “**prime editing**”. Prime Medicine, a biotech firm will shortly trial this. The product consists of Cas9 nickase (“scissors”), with a precise RNA guide, and a RNA template or “instruction” of the desired change, to be used by another attached enzyme called reverse transcriptase, which reads the template and synthesises the correct DNA sequence in the right place!!

As **prime editing** could replace long stretches of the genome it could become a “broad” treatment for a range of rare diseases where the errors are in the same region. If this is the case affordability could be less of a problem.

“**Bridge RNA**” is another new technique designed to add, remove or invert. large stretches of DNA.

Certainly, these new techniques will have to overcome many technical and safety tests. And with one-time shots of product currently costing over \$1 million, (needed in order to recover development and trial costs), we’re not going to see many recovered patients soon. However, the pace of research and development of these techniques is astounding. and there are tangible reasons to be hopeful.



In short.....

The Editor

Most holidaymakers are going home when they planned to, but not all!

Astronauts Butch Wilmore and Suni Williams were to return in June from an 8 day "sightseeing break etc" in International Space Station. But a glitch with their Boeing Star Liner, (on its first manned flight) seems to have delayed things. "Of course they're not stranded in space", insists NASA. But they may have to get home on the competitor's craft SpaceX which plans to dock later this month and not return until next year!

As in our industry, Quality Assurance is vital.

