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NEWSLETTER

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In this Edition :

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T CELLS & T REX

A Comparison of 2 Organisms
By The Editor

At first sight, these two organisms have little in common. The difference in size is enormous and one of the organisms is extinct, whereas the other one is found in most species.

But there are things they have in common:

1. Both organisms are / were very aggressive.
2. They attack targets they recognise.
3. Humans are fascinated by them – as children in museums, and as scientists in research.
4. In both cases, the T could stand for THREAT.
5.

One is known for reducing anything moving in the neighbourhood to mincemeat, the other (T Cells) being the “enforcers” one of the most important types of white blood cells in the immune system. There are different types of T cells, and one named CT8+ can truly be called the “killer cell”, able to kill virus infected cells, & cancer cells.

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Whereas one wouldn't try to train T Rex; researchers now think, and find, it's possible to "train" or reprogram these T cells to attack cancerous cells they don't currently recognize. The key features that research is exploiting are that:

- T cells have T cell receptors on their surface and
- harmful cells have specific protein markers called antigens on their surface.

The cells of many harmful diseases that the patients CT8+T cells don't currently recognize, also have specific protein markers on their surface.

For these, a treatment called CAR- T, (short for "Chimeric Antigen Receptors") holds out enormous promise. Already several CAR-T cell therapies are licenced to treat leukaemia and lymphoma. Its promise could extend to diseases from heart conditions to asthma, which share similarities with cancer cells, autoimmune diseases, and many chronic illnesses related to ageing.

In the reprograming of the patients T cells a new gene, encoding a chimeric antigen receptor, is added to these T cells. This receptor is aimed at the specific "target" antigen of the disease-causing cells. "The right key in the right lock".
The procedure involves T cells from a patient's immune system being extracted, genetically tweaked to give them Chimeric Antigen Receptors that can find these antigens. The tweaked cells are then returned to the patient's body, to start work.

"Home Made or off the Peg"

You may have spotted the fly in the ointment. The big problem is that the T cells which are reprogrammed can only come from the patient, (otherwise there's immune rejection). Then they have to be cultured, purified and isolated from the culture medium, before being reintroduced to the patient's body, a process which can take several weeks and is extremely costly.

So, the next phase of research is to explore ways of bringing the cost down to Earth from the astronomical level of around $400,000. Here two possible lines of attack are envisaged. The 1st is to find a way of using reprogrammed T cells with "universal" applicability against a certain disease. And the second ambitious idea is where the whole CAR-T procedure occurs within the patient's body, adapting the trick of mRNA vaccines.

PHARMACEUTICAL CANNABIS EXPANSION IN MOROCCO

Dr Mohamed Said MASRAR
Industrial pharmacist. Expert in pharmaceutical development

The strong international interest in the potential of cannabis for ethical pharma products has turned the spotlight onto Morocco given the country's historical association with its cultivation. The Kingdom is the world's leading producer of cannabis says the UN, and has now set itself the objectives of:

1. Combating drug trafficking,
2. positioning itself on the global market for legal cannabis
3. spurring economic advancement in the Rif, where the plant has long been cultivated.

In 2021, Morocco adopted an important law, n°13-21, setting a new direction for the industry. The law governs the industrial and medical uses of cannabis, under which are authorized:

- The cultivation, production, & exploitation cannabis & derivatives from only three deprived rural provinces of the Rif, (although other areas could be opened up).
- The export and import of seeds, the creation & operation of nurseries, cultivation, processing and manufacturing, transportation, marketing, product import & export.
- Such activity only in pharmaceutical establishments governed by codes in Law 17-04, and restricted to cannabis whose THC level exceeds 1%,
- Pharmaceutical establishments must establish mutually exclusive harvest contracts with growers, be cGMP compliant, and use standards defined in 13-21.

(This Act comprehensively changed both the 1922 Law restricting use; and it's 1954 amendment aimed at combatting drug addiction and limiting use to medical and scientific purposes only).

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ANRAC, the National Regulatory Agency for Cannabis Activities implements the intent of the 2021 Law, and is responsible for controlling all industry stages, from seeds & the certification of plants to the distribution & marketing of the products. **Anrac's role includes licensing** national and international operators in the legal industry.

The Medicines & Pharmacy Department handles registration procedures. However, a production unit must have GMP authorization, following review of the equivalent of Site Master Files et al.

Law 13-21 marks a decisive turning point & opens new perspectives for the pharmaceutical industry and agriculture. It aims to stimulate the local economy and promote medical and industrial research. Previously it's estimated the small Rif growers received only 4% of the (illegal) market value of products, compared to potentially 12% in the legal market.

The growing opportunities in cannabinoid APIs, medicines, food supplements and cosmetic products have now brought needed prosperity to local producers, with income of $241.2 million expected in 2024. The Moroccan pharmaceutical industry forecasts a 10-15% share of the european market for cannabis-derived products, and we estimate a share of $650 million. The global market is estimated at $20 billion, 80% recreational products, dietary supplements and cosmetics, & 20% medicines. Morocco has trade agreements with the EU & US.

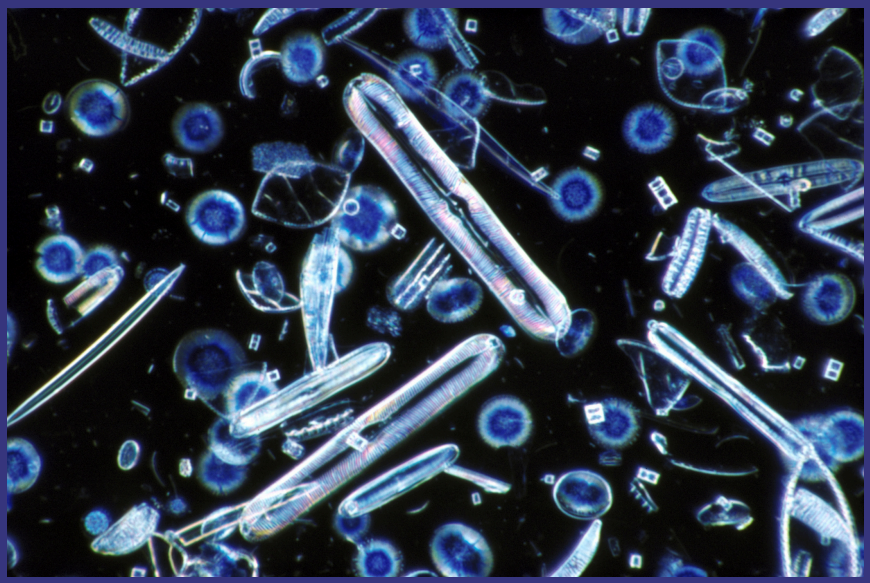
Don't hesitate to contact Galenisys and its experts for help with viability studies, authorizations, and the design of compliant production units for these products, or other pharma products.

Mohamed Said MASRAR

WATER SYSTEMS - WATER FOR INJECTION?

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

Since the earliest forms of life evolved in water aeons ago, it's not surprising that organisms are able to take every opportunity to proliferate in this medium.



Every aspect of pharmaceutical water systems needs to be considered so that they can continue to remain contamination free. I recall a brand new WFI system for a manufacturer of biologicals, which had been designed and constructed by one of the world's leading engineering companies, gave the client problems after entering use.

The head of QA asked us to assess the system &troubleshoot the issues that were causing contamination within it. Their Quality Control were finding coliforms and other gram-negative bacteria in very high counts at a number of use points. This was hard to understand since distribution temperature was at 85 degrees C. We checked their testing methodology which was fine.

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Our physical inspection of the system found a few sagging pipelines and some rather long dead legs. However, it was our observation of the procedure of sampling taking which revealed the cause of the contamination.

All Use Points were being capped after use and rinsed with cold water. The capped Points were left during the night and tested the following morning. This gave plenty of time for the contaminants to proliferate in their preferred environment, and so it was not surprising that high counts were detected subsequently.

Our recommendation of not rinsing nor capping the Use Points, but allowing them to dry was acted, on and solved the issue.
And for good measure we had the above issues with design and construction corrected.

It's important to keep your eye on water systems. They may be sound, or vulnerable, as constructed. During their life, their maintenance or use may change because of modification, negligence, or familiarity. So, if you've got a water issue already, or want to avoid one, call Galenisys for an assessment.

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The Project Manager's Notebook.

In this, the fourth article in my series, the theme is WHO does What.
By Aubonne

In the very popular American series “The Flintstones” the regular punchline was “Whose baby is it”? It's essential that the Project is clear about who does what. No two projects are alike, & each will certainly involve people who've never worked together before, possibly from different cultures - and in international projects speaking different languages. So, the project structure in human terms, needs to be defined, documented, and understood.

The Project Structure

Parts of the project structure may already be obvious from the nature of the project and profile of the client. A large international company may well have its own project department, QA & validation specialists. Whereas a biotech company whose strengths are in R&D will wisely use the services of experienced external contractors and consultants for eg production plant construction.

Subsequently a documented “Responsibility Matrix” is a good means of clarifying things in detail eg action by Client, Architect, General Contractor, Consulting Engineer, Package Supplier etc.

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Control & Reporting

The project structure determines the logical authority, accountability & reporting hierarchy. Typically, at the top will be the Sponsor, or the Supervisory Committee. They will normally receive a Monthly Report by the Project Director / Manager, (the equivalent of the CEO in an ongoing business) on:

1. The Financial Status against Budget; for both commitments and for cash flow.
2. Project Status against Project Plan together with forecasts which take account of the current situation.
3. Issues beyond the Project Directors authority, requiring resolution.
4. Health & safety, personnel items, etc.

The functional heads of the various disciplines & contractors, involved in the current phase of activity, will feed in their progress reports & problems at the Project Directors Meetings. More detailed meetings - weekly, or even daily - to thrash out bottlenecking, technical issues, delays & "workrounds" will need experienced meeting management to avoid them becoming all consuming.
Occasionally there will be issues arising beyond the competence / authority of a meeting. Such Cost / Time / Scope trade-offs need to be cascaded UP for resolution, not hidden.

Information Flow

In our well-run meetings, they started at 8am, Minutes were taken by the last person to arrive – ensuring punctuality - & to be distributed by midday! Reporting back was only by exception (all other actions identified previously, were considered "completed").

Pharma projects will frequently involve hundreds of people at different stages. For good control and reporting, it is important that the people involved are kept up to date (with reports & planning updates) and thus able to respond and report back usefully.

By the way, it's essential that work breakdown structure package* contracts include the obligation that a responsible executive of package suppliers attend the (monthly) meetings run by the project director (if required).

Getting a sound Project Structure established at inception is a key to success. That requires an understanding of the project scope and objectives, and an appreciation of the human resources required to achieve it.

The Galenisys Team have wide experience in varied Pharma Projects and will be happy to assist you resourcing yours

* see Galenisys September 2024 Newsletter

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BETTER FOR LONGER.

Using "old"pharmaceutical products well after the expiry date.
The Editor

In recent years in Europe and the USA, there have been warnings of shortages and actual shortages of key of key medical products, in particular painkillers such as paracetamol and antibiotics such as amoxicillin.

We have written about the different causes of shortages in earlier newsletters. They include "offshoring", epidemics, and the low prices in Europe offered to generic manufacturers. It's therefore pleasing to report that one relatively low cost help is perhaps to extend the official shelf life of existing products including those in your pharmacy cabinet.

In a recent article « Que Choisir Sante », a French consumer magazine, published the results of a limited analysis of various samples of paracetamol and ibuprofen taken from consumers medicines cabinets. The analysis of 30 product samples showed that they retained a level of active ingredient at least 90% of that present when manufactured, in 80% of the samples, for at many years beyond their stated expiry dates.

Similar limited studies from Germany and California showed that samples of products manufactured decades ago, in many cases still retained levels of active ingredient more than 90% of the original

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In the USA and in Europe the authorities maintain emergency stocks of medication to be used in the case of exceptional events such as epidemics or terrorist attacks. Given the cost of these, they also are interested in ensuring these are usable as long as possible. But Que Choisir report slow progress in the discussions of the French ANSM and manufacturers, on extending stated shelf life.

The FDA conducted a 20 year programme which reported in 2006 on 3000 batches of products composing, 120 categories of treatment. It was reported that in 88% of these their expiry date could be extended by at least a year, still retaining an active ingredient level of at least 90%. These included the important products amoxicillin, present in Augmentin and Clamoxy - an extension of 23 months, physiological serum, & Betadine 6 years, and paracetamol -pseudoephedrine 2 years, for example. (For reference, the upper & lower allowed limits in most cases are 105% and 95% in Europe, and at least 90% in USA).

As consumers, we obviously need to take the same precautions in assessing whether to use that “old paracetamol” in the same way as we look at meat or yoghurt. If its been correctly stored we can use smell, taste, and appearance in deciding whether to use that box of ibuprofen that expired last year instead of rushing out to find the all night pharmacy.

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