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NEWSLETTER

Tony Dunford Editor

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The Project Manager's Notebook.

by Aubonne

A new series of articles by one of our Pharma Industry veterans, comprising (fairly timeproof) 1st hand Notes, Anecdotes & Lessons from Projects across the globe.

1 HOW MUCH? - Getting the cash.

The first major milestone in any project is to obtain approval for the Capital Expenditure required.

In the Budget?

Although there will always be occasions when unbudgeted projects get the green light, getting approval is much easier if the project is already in the Budget established in the preceding financial period. (No adverse surprise for the Finance Department). In a well-run company, cash is not left “lying around” but put to work.
So, during the Budget Exercise work with the heads* of the departments whose needs will trigger capital projects, to understand rationale, requirements, & rough out estimates.

Financial thresholds.

Your company may well have “Threshold Requirements”: “Discounted cash flow rate”, “Net Present Value”, “Return on investment”. If they don't have, maybe you should run the finance department as well as the project. (Back in high inflation years I liked to show my projects had a 2-year payback). If it doesn't meet threshold the Project may still be worthwhile or necessary, but the rationale needs to be solid & endorsed *.

A Design Phase?

It may well be that the capital required is relatively large, but the estimates are “iffy”. In this case, put forward a project to cover the design phase and get a more accurate cost. During this the eg commercial / sales / or marketing case could be firmed up.

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Confidence

Gain the confidence of the Directors by establishing a track record of project delivery on budget & on time. In smaller businesses keep direct contact with the boss to advise of upcoming likely projects.

Know about Cash Flow

Projects have a typical cash flow profile over the period of project implementation. Typically it starts off relatively low during design stages, building as site preparation begins. It reaches its high rates with down payments on large equipment long lead time items; and when there are stage payments to major construction package contractors. Cash flow rate tails off during commissioning and qualification. Project Literature will provide some examples curves.

Demonstrate good husbandry.

Part of confidence building is showing that you have used the Company's' resources responsibly. It may well be that part of your site (or equipment) is no longer in use following volume decline of a certain product. If the new project can use these assets, then do mention this in your Capital request.
For example, we needed to integrate an additional product in house which had alcoholic extraction in the process. This necessitated a separate building with flameproof electrics, since the main facility had non flameproof electrics. When this product, was later discontinued the separate building was converted – at relatively low cost - into an onsite rabbit house for pyrogen testing, which also needed to be segregated from the main facility.

In next month's Galenisys Newsletter, we'll look at the factors involved in building the total Pharma Project cost for Capital approval.

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Why Bacterial Contamination of Non-Sterile Drug Products occurs so easily

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

Last month I emphasised the importance of well designed, & maintained water systems, good manufacturing practices, & water sampling techniques, in combatting Burkholderia cepacia contamination of non-sterile water-borne products containing preservatives.

Here's why B.cepacia and other gram negative organisms can survive or multiply in a variety of non-sterile aqueous drug formulations.

In water systems, gram negative bacteria can use nitrogen and carbon dioxide from the water and multiply causing a risk of contamination to the product formulations and the formation of biofilms in the water system itself. (We will provide a further article on bio film formation in later editions).

Drugs that contained preservatives or had intrinsic antimicrobial properties have been contaminated with B.cepacia and other gram-negative organisms. These organisms persisted and even multiplied in these drug products. As a result, microbial growth emerged later in the product's shelf-life even though the batch met microbiological specifications at the time of initial release testing.

In essence these bacteria are resistant to certain preservatives and antimicrobial agents and cannot compensate for poorly designed and maintained water systems nor for insanitary or substandard manufacturing practices.

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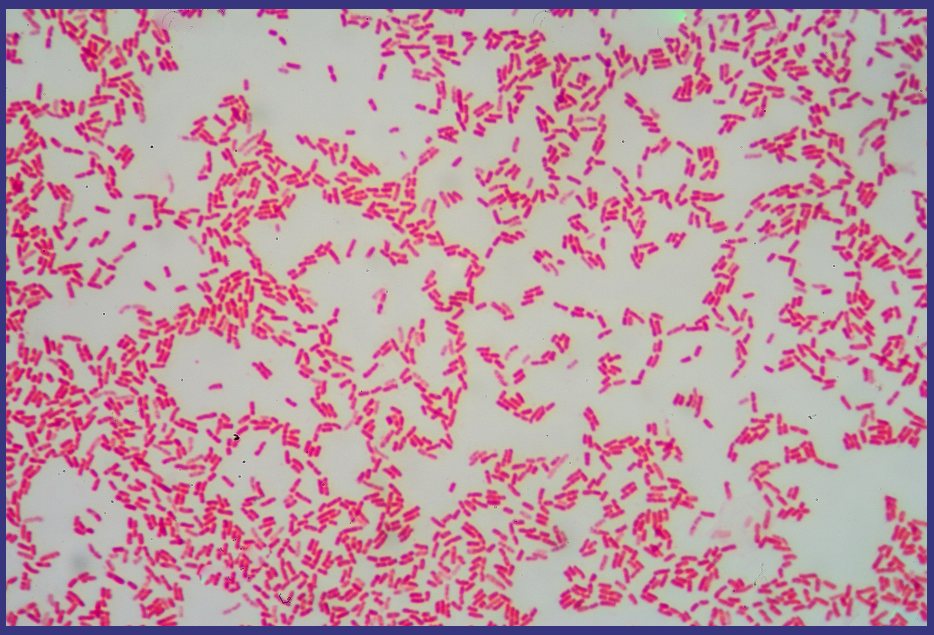

Additionally, when an operation fails to meet cGMP requirements, the level of microbiological contamination introduced during the course of batch production is unpredictable, and test results from separate samples taken from a batch can vary widely.

Because of this uneven distribution of microbial contamination across a batch, relying on quality control sample testing may not detect unsafe batches. The nature of contamination, and risks posed by contaminated drugs, underscore the importance of the cGMP requirement to design utility systems and manufacturing operations to prevent contamination with microorganisms, such as B. cepacia, that are objectionable in view of the intended use of a drug.

Hence also the need for manufacturers of water-based non-sterile drugs to be aware of the contamination risks for their products, and to design and implement a robust contamination prevention and control programme.

Steve Biddulph

Galenisys can use its many years of experience and technical expertise to assist companies in performing risk analysis on their manufacturing processes and to design and implement contamination prevention and control systems.

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COMPLIANT MEDICINAL CANNABIS PRODUCTION FOR EU COUNTRIES

By " Ibericane"

Our guest author is a Graduate Biochemical Engineer with Director level responsibilities for Compliance & Control.

Across Europe, countries are publishing laws and regulations related to medicinal cannabis. There is no doubt of the potential of medicinal cannabis, nor that it is a lucrative business for products with an exponential increase of future demand.

Some investors wish to invest but don't have the technical knowledge related to the heavily regulated market that is the pharmaceutical industry.

The challenge is that as medicinal cannabis is a herbal medicinal product, there are additional concerns related to the degradation and reproducibility of product.

Too Strong ??

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The Good Agricultural and Collection Practices ("GACP") requirements for herbal medicinal products cover Quality Assurance, Personnel and Competencies, Facilities and Equipment, Documentation and Production.

For medicinal cannabis – considering that we are dealing with a controlled substance – in October 2023, the European. Pharmacopoeia. Pub published a standardised monograph for cannabis flowers.

This will apply from 1 July 2024, replacing the current monographs (in NL, DK, D and CH). The monograph will thus form the basis for the testing of medicinal cannabis in Europe.
We will be hearing about new developments to the GACP, as the guideline is currently under revision.
Ibericane.

Galenisys staff have provided support to various companies using controlled substances in their process, to ensure their compliance.

And across the Lifesciences Industry we have been involved with registration processes, the design and construction of facilities, the implementation of QMS, preparation for inspections, audits of suppliers and internal audits, which will also be precursors of medicinal cannabis production in Europe.

Evolution versus Innovation

The Malaria Wars
by The Editor

The centuries old battle against malaria illustrates in a fascinating way the ongoing struggle between natural evolution and human innovation. On the evolutionary side, we've got parasites in the mosquitoes and new species of mosquitoes. Recently, the two protagonists in the Malaria Wars have wheeled out new weapons.

This is the line up since the wars began, in approximate chronological order (until the last couple of centuries humans invariably lost),

Natural Evolution	Human Innovation
Swamps & marsh lands	Drainage
Stagnant Water	Good sanitation & larvicides
Mosquitoes	Insecticides
Human proliferation ie abundant mosquito food supply	Mosquito nets
Mosquitoes & embedded parasites	Anti-malarial drugs
(Civil wars & failed states)	(Almost universal) Education
New Mosquitoes strains (NEW)	Dual insecticide nets (NEW)
Drug resistant parasites (NEW)	Anti parasite vaccines (NEW)
Climate Change (not so NEW)	“Neutered” mosquitoes (NEW)

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Recently the “wars” have heated up, with again, huge cost and suffering (particularly in Africa with 95% of cases & 97% of deaths), Estimates in 2021 were of 247 million infections and 619,000 deaths, globally ascribed to malaria. This article looks at how the above “NEW” factors have helped or could help each of the 2 “sides”.

New Mosquitoes strains

Anopheles stephensi is an invasive Mosquito species for Africa. It recently has crossed over to Africa from the Arabian Peninsula where it is endemic. It is also native to parts of South Asia and the Arabian Peninsula. The first recorded outbreak was in a city in eastern Ethiopia in 2022. This species has got different characteristics to its cousins, for example, it bites earlier in the evening (before people are under their bed nets) and its larva also easily multiply in water tanks and old water bottles. A key battle is stopping it spreading across all Africa.

Dual insecticide nets

In 2017, WHO started to recommend the new type of insecticide-treated nets (“ITNs”) that combines pyrethroids with piperonyl-butoxide (PBO), and enhances the potency against resistant mosquitoes. (These were developed & produced by The New Nets Project (NNP) in which The Global Fund and Unitaid each invested US$33 million between 2018 to 2022. It is believed that “compared to standard nets, the introduction of 56 million dual insecticide nets in 17 countries across sub-Saharan Africa averted an estimated 13 million malaria cases and 24,600 deaths”).Previously nets were only treated with. pyrethroids to which some mosquitos had become resistant.

In March 2023 the WHO published new recommendations, in Guidelines for Malaria, covering 2 new classes of dual ingredient ITNs with different modes of action:

- Pyrethroid-chlorfenapyr nets combine a pyrethroid and a pyrrole insecticide to enhance the killing effect of the net.
- Pyrethroid-pyriproxyfen nets combine a pyrethroid with an insect growth regulator (IGR). The IGR disrupts mosquito growth and reproduction.

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Climate Change Is "doing what it says on the tin" & means that the temperatures are rising in Africa too. (Of course, climate change is not exactly new. There was abundance evidence presented for it more than 30 years ago. But it was disputed & ignored).
As mosquitoes struggle in temperatures above 28°C, some parts of Africa might suffer less. But the continents previously cooler Highlands, until now unaccustomed to the challenges, now have a greater vulnerability (the longer transmission season). Devasting floods such as in Pakistan in 2022 meant that plenty of stagnant water was around & healthcare resources were occupied with other problems. Similar future floods are likely to cause future outbreaks.

Drug resistant parasites
Although mosquitoes get most of the blame, the culprits are the 5 Plasmodium species of parasites. And in particular the Plasmodium falciparum, "which (causes) 90% of cases and may be lethal, though geographically widespread P. vivax also causes significant morbidity".*

Anti parasite vaccines
The first WHO-directed malaria vaccine implementation studies have started to chart the best approaches using the leading malaria vaccine to date, the RTS,S vaccine. RTS,S/AS01 is the first malaria vaccine to be tested in Phase 3 clinical trials and assessed in routine immunization programs in malaria-endemic areas. (The RTS,S vaccine was created in 1987 by collaboration between GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) RTS,S/AS01 vaccine was developed by a public–private partnership in 2001 between GSK, and PATH's Malaria Vaccine Initiative - with the Gates Foundation funding)**.

The future :
"Bednets, vector reduction, various drug regimens, and, most recently, the P. falciparum RTS,S vaccine, are means of control, but new strategies are clearly needed. Among the candidates are long-acting injectable antimalarials2, which for chemoprophylaxis have aptly been termed "chemical vaccines" *.

Let's hope we'd hear more of these innovations above the low evening whine of the old enemy.

The Editor

References
*"Clinically relevant atovaquone-resistant human malaria parasites fail to transmit by mosquito" NATURE 12/10/2023
** Human vaccines and immunotherapeutics. Volume 16. 2020.

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Galenisys up date

- Our current activity includes continued Support to our Middle East client. Construction on their manufacturing site is moving forward with foundations now laid. The detailed Project Plan has been approved, and the major items of manufacturing equipment ordered.
- Galenisys have concluded an initial Consultancy Services contract with a major Swiss based life sciences company.
- And we continue to provide Auditing and On Site Assistance to an American based company, at sites both in Europe and the USA.