Galenisys 11 rue Notre Dame de Nazareth , 75003 Paris, France. Tel : +33145554414 or +33632329927

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NEWSLETTER

Tony Dunford Editor

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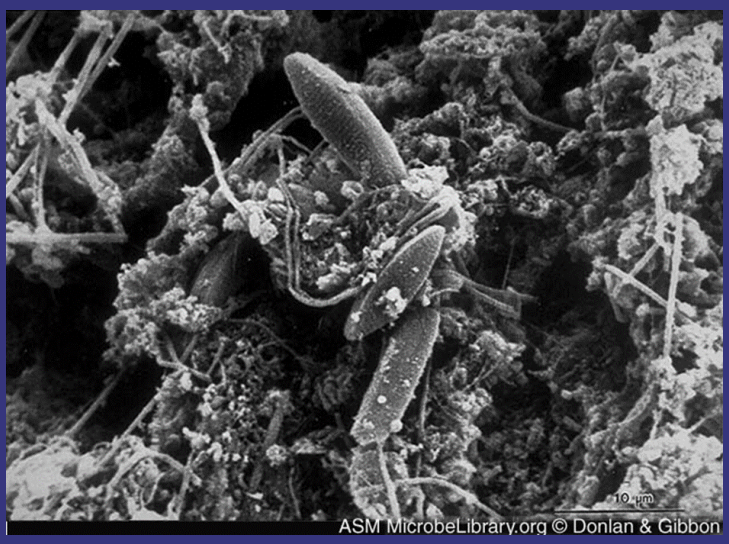
Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

THE DANGERS OF BIOFILMS

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

There's a tendency to think that bacteria float around on their own and don't exist in clumps. Maybe this is because they've been found everywhere from under our feet, to miles beneath the earth's crust, or from ocean depths to Everest.

But in fact, vast numbers of them exist in colonies called biofilms. When a solitary bacterium finds a nice source of food, it secrets sticky compounds to anchor itself to it and begins to divide. Within a very short period of time a small colony of descendants spread out and eventually form visible films.
(See the electron microscope scan below).



As you can see, biofilm consists of bacterial cells embedded in other materials and debris such as mineral crystals, corrosion, soil, silt, and even different blood cells, depending on where the biofilm is found. Until recently biofilms were poorly understood but now a variety of research companies are making inroads into this zone of ignorance.

t appears that the biofilm is built up using a process by which the bacteria exchange messages with neighbouring populations and adjust their behaviour accordingly. The result equates to a multicellular organism, comprising the billions of individual bacteria, having the means to transport carry nutrients and remove waste.

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We tend to know biofilms as plaque on teeth, or the slimy substances one finds behind sinks, or on metal surfaces of moored boats, (and even moving vessels).

However, they are also present in dangerous places – eg on hospital bed rails, laboratory incubators; and, importantly on poorly designed purified water and WFI systems.

For patients their effects are serious: they infect open wounds, clog up catheters, & form film on internal joint implants. Such problems cause huge extra expense for health services.

Strength in numbers

The film cohesion ("stickiness") makes it much harder to remove bacteria than if they existed as individuals. Hence the biofilm protects many of its constituents from antibiotics, disinfectants, and human immune cells, which struggle to penetrate the whole film. As sections of the biofilm can break off during "an attack" - and also since they can exist as clumps floating in liquids – complete eradication is really problematic.
For patients the conventional response is typically cleaning open wounds, prescribing antibiotics; or removing infected implants, sterilising them, and replacing them in the human body.

Now research is focusing on the use of certain viruses known as **bacteriophages** which can infect bacteria in the same way as bacteria affect us. Fortunately, **"phages"** leave the host cells alone like antibiotics, but unlike antibiotics **they replicate themselves** in the process of killing the bacteria so small doses can generate very effective swarms. And of course, being viruses, they also can evolve promptly to counter evolving bacterial defences.

To date there are only a handful of promising early-stage laboratory studies pointing to the use of phages against bacterial infection.

Poorly designed purified water and WFI systems are prone to biofilm which is not only difficult to remove in the early stages of formation but impossible to do so once the biofilm matures. The mainly gram-negative bacterial cells to be found in biofilm form the "sticky" polysaccharide coating that is extremely hard to remove. The dentist periodically removes it from teeth with a drill, but you cannot do that in your water system!
Once biofilm develops in a water system then usually the pipe work and other elements must be removed and replaced - a very costly & disruptive exercise.

As a result of our considerable experience of helping clients needing 24 / 7 purified water and WFI systems, Galenisys can provide invaluable assistance in ensuring the system design and operation that will prevent biofilm build up.

Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

KNOWHOW COUNTS

By The Editor

No sooner had we “gone to press” with the February Newsletter and its’ article about obesity and Wegovy; than the news came that Novo Nordisk were running out of capacity for this blockbuster. (Success brings its own problems!). Novo Nordisk's solution was straightforward: **buy regulatory approved manufacturing sites with the knowhow.**

The explosion in demand for the weight-loss drug has led to the holding company buying New Jersey-based firm Catalent for $16.5bn (£13.2bn) to increase capacity.

The deal comes as the popularity of Wegovy, (used by celebrities including Elon Musk and Oprah Winfrey), and Ozempic Novo Nordisk’s diabetes drug, continues to grow, helping to cement the Danish drugmaker as Europe’s most valuable company, with a market value of about $500bn. Obesity drug sales at Novo Nordisk jumped by 154% to £4.8bn last year, with Wegovy accounting for £3.6bn of that.

The two drugs have proved popular in the US, particularly Wegovy, with Novo Nordisk estimating that 1 million Americans have used the drug since it was approved in 2021 and 600,000 currently using it.

But as this demand outpaced the company’s manufacturing capacity it has led to the supply problems.

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Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

BUYING MORE FILL & FINISH CAPACITY

Novo Holdings will buy (from Catalent) and then immediately sell three of its sites for $11bn in US and Europe to Wegovy Novo Nordisk, to "... make sure there is broader rollout for Ozempic and Wegovy, (by) enhanced capacity" specifically the Catalent fill-finish sites in Anagni (Italy), Brussels, and Bloomington (Indiana, US) for $11bn. The deal means the sites will now exclusively deliver Novo Nordisk drugs.

This news reminded me of a hectic period early in the career of myself and a colleague here at Galenisys, when we were drafted in to a recently acquired European contract manufacturer who had got into difficulties with the FDA. Their 483 letter followed the adverse pre marketing approval inspection of the facilities.

Whilst managing the routine on the site, our principal job was to win FDA regulatory approval so the site could start to manufacture our sterile products destined for the American market. (This we did after some 2 years of CAPEX and beefing up QA).
The "regulatory win" also boosted the sales and profitability of our Contract Manufacturing business, as clients were willing to pay for compliant QA and to avoid "regulatory risk".

Together with other industry experts we have noticed an increased recent reliance by a major pharma companies on CDMO's and CMO's for capacity, expertise, and regulatory compliance.

The value of the Novo - Catalent deal far exceeded the cost of the factory we bought, but what remains unchanged is the fact that a facility (whether CMO or inhouse) with the necessary manufacturing expertise, AND FDA regulatory approval, is a very valuable asset - because it has maintained a compliant and effective Quality Assurance system.

Galenisys are pleased to have Catalent amongst its clients.
The Editor

Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

NEWER, CRISPR, AND GOOD FOR ORPHANS

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

On 16.01.2024 the European Medicines Agency EMA published "Human medicines highlights 2023", which gives a short summary of the medicines the Agency approved in 2023. (77 gained marketing authorisation for the European Union).

One of them was the first **advanced therapy medicinal product** ("ATMP"), using the ground-breaking gene-editing technology known as CRISPR/Cas9, to treat two rare blood disorders.

The repeated sequences (strands), known as CRISPR*, in the DNA structure were first identified in 1987. Since then, it's been a long journey to this first positive opinion from EMA for a medicine produced by the resulting technology.

Years of fundamental research in genetics were needed to understand the purpose the CRISPR inside the DNA, and the structure of the Cas genes which preceded it. Then it needed insight to appreciate the sequences as an immune tool. Finally came exploitation of CRISPR editing in gene therapy.

The name of the (conditionally) approved** orphan medicine is CASGEVY, for the treatment of transfusion-dependent β-thalassemia (TDT), and sickle cell disease (SCD). It's a product of Vertex Pharmaceuticals (Ireland) Limited.

Casgevy will be available as a dispersion for infusion and is intended for one-time administration. Its benefits are the ability to eliminate dependence on chronic red blood cell transfusions in patients with TDT; and to reduce the number of vaso-occlusive crises in patients with SCD. (The downside is the side effects of the other medicines required for the modified blood cells to engraft and replace the unmodified stem cells).

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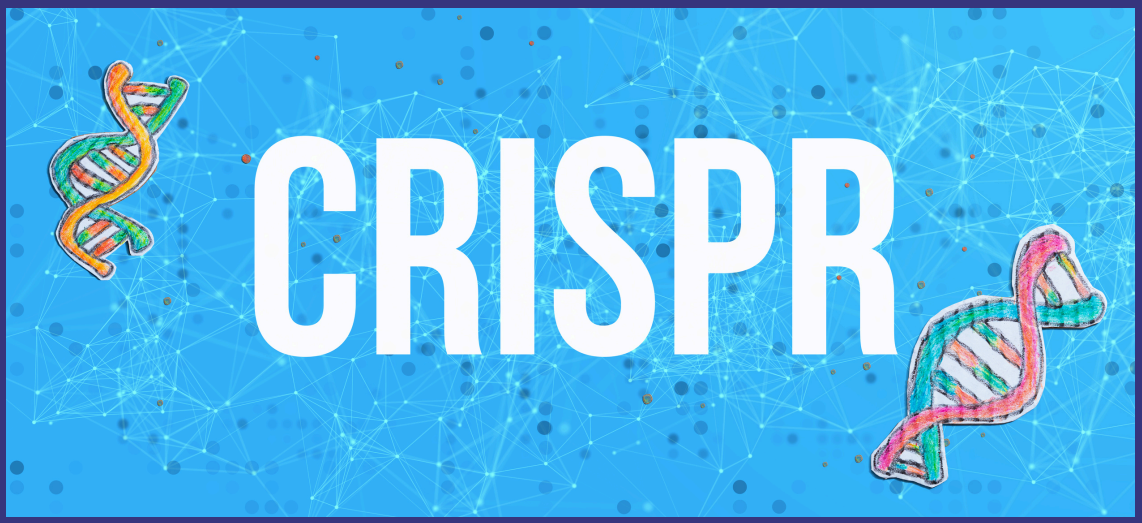
Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

CRISPR/Cas9 technology edits patients' cells in vivo. When transplanted back into the patients, the edited cells correct for the absent haemoglobin A in patients with TDT; and for the aberrant haemoglobin S in patients with SCD.

So ATMPs are already here! Soon other entities will be based on new information & technologies such as:
-Viral Gene Therapy and Vectors development
-Plasmid transfection
-New Cell lines
-Gene expression
-Enzymes
-Nanoparticles

* CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats (You have to know your acronyms these days!)

** The Committee for Medicinal Products for Human Use ("CHMP") adopted a positive opinion, recommending the granting of a conditional marketing authorisation. As Casgevy is an advanced therapy medicinal product, the CHMP positive opinion is based on an assessment by the Committee for Advanced Therapies.



SHORTAGES of MEDICATION

By The Editor

Some years ago, a pharmacist friend of mine in semi-retirement, who was QP for a local contract manufacturer of generic analgesic tablets, invited me to visit the facility. Several light bulbs in the reception area needed replacing, there was sterilised milk in the canteen, and the boss drove a 12-year-old car.

Evidently prices were not very high and the key to solvency was tight control of expenses. Investment was largely limited to the fastest tableting and packaging machines that were affordable, in order to keep down unit costs. Some pack prices were less than a tube of “Smarties”.

There must be a graph somewhere of the average number of tablets consumed pa as people age. I imagine the line tends to the exponential in later age decades. In developed countries we know that people are living longer so it's easy to figure out that unless manufacturing capacity is sustained, and expands, the likelihood of shortages will increase. We seem to be in this situation already.

In the **USA** the website Drugs.com lists the 475** or so “current” shortages, (**those notified in the period 2022-2024 & still scarce).

Medicine shortages by month in the **UK** have doubled in the past two years to 96 (data at 16.12.2023 for “supply issues and discontinuations”) according to the British Generic Manufacturers Association. The NHS and press currently detail shortages of medication for ADHD, HRT, antipsychotics, and epilepsy medicines eg carbamazepine “Tegretol”, and Oxcarbazepine (“Viatris”).

The Epilepsy Society lists the shortages of some 17 epilepsy medications since June 2023. It includes Vigabatrin (« Sabril”) 500mg tablets. A typical sufferer maybe on 2 tablets a day for 50 years which is a lot of tablets.

Sanofi said this shortage was due to a delay in the **global supply of the active pharmaceutical ingredient** used to manufacture vigabatrin. The MHRA issued a batch recalls of Sabril tablets and Sabril granules (vigabatrin) in July 2023, as a precautionary measure, due to the **detection of traces of tiapride in batches of the manufacturers API - vigabatrin.**

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In early January the Dept of Health advised that supply of glucagon-like peptide-1 receptor agonists, used by those with type 2 diabetes, would be problematic throughout 2024, and that doctors should immediately stop prescribing it for weight loss. A national patient safety alert requiring "action to be taken by providers to reduce the risk of death or disability" followed.

In Europe, a recent European Association of Hospital Pharmacists survey reported that 95% of hospital pharmacists across the continent were experiencing shortages. An EU working party met in December to discuss the critical shortage of key medicines.

Various analyses of the problem, clearly point to a range of accumulating factors including:

- The offshoring which has taken place over recent decades
- the vulnerability of these extended supply chains to physical disruptions (eg national export bans, and violence in the Red Sea currently).
- poor Quality Assurance in Southeast Asia and China where many APIs are now manufactured, in some cases exclusively. (The EMA recently recommended the suspension of usage of about 400 medicines tested by an Indian laboratory).
- the impact of the war in Ukraine.
- and for the UK, the extra regulatory paperwork for some imported goods due to Brexit

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Steve Biddulph +33 6 32 32 99 27 Steve.biddulph@galenisys-pc.com

Fundamentally the issue in Europe & UK is the low prices paid to local generics companies by Governments, and supermarkets, which has caused many manufacturers to discontinue products. The response in Europe and the UK seems to be that the answer to shortages is to keep prices squeezed; whereas classical economic thinking recommends price rises & predictability, to increase supply resilience.

I**n the UK** The Government "voluntary" scheme introduced in 2019 to limit NHS spending on branded medicines to < 2% in a year. As 2023 ended, there was a 26% levy on revenues of drug manufacturers earned beyond the cap.

The companies claim it has made the UK an unattractive place to do business acting as a drag on investment. From this year that cap will rise to allow a 4% annual rise in spending. **The British Generic Manufacturers Association** says the government is still penny pinching.

In our April 2023 Newsletter in we reported on the amoxicillin and other shortages in Europe, with quotes from key players:

1. **Spains' generics manufacturing association** stated half the generic medicines sold in the country are priced below 1.60 euros per box or bottle,
2. **Germany's generic drug association Pro Generika** said there, (the biggest generics market in Europe), the average amount manufacturers receive has fallen 66% over the past decade.
3. Reuters resumed the situation as follows:

- Low generic drug prices mean razor-thin margins for firms
- Companies say they cannot boost output enough due to costs
- Making generics in Europe may become unsustainable.

Has anything changed from this?

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