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NANOTECHNOLOGY: A PATHWAY FOR SUSTAINABLE INNOVATION IN DRUG DEVELOPMENT

Here, Andrea Cusack, Chief Executive Officer, leon, discusses how, by using bottom-up nanotechnology techniques, efficiencies can be found both in the development of new chemical entities and in the repurposing of existing drugs, and how these efficiencies translate into reduced energy requirements and therefore more sustainable industry practices.

It seems that, across industries, every effort to go green requires some sort of compromise be made, whether that be on price, performance, stability or any number of other factors. For example, at the time of writing, electric cars are more expensive to buy than those with a conventional combustion engine, and they can't go anywhere near as far. Of course, we all recognise that very soon such compromises will become less pronounced, as the drive towards a more sustainable world gathers pace, and consequently green alternatives and solutions improve in performance.

However, there are already some areas in the pharma supply chain where going green need not cost the earth in terms of performance. In this article, we will explore how bottom-up nanotechnology can deliver oral and injectable APIs with enhanced bioavailability, increased solubility and improved stability, sustainably.

We will also take a look at the sustainability challenges that the current "gold standard" approach faces and demonstrate how bottom-up approaches to nanotechnology require a considerably lower equipment footprint, leading to a significant reduction in energy consumption. All of which is achievable without any compromise on performance, timescale or cost.

SHIFTING TO LOW-CARBON STRATEGIES

From the ice caps to the rainforests, there is no shortage of ready evidence reminding us that today's global economy can have a very direct impact on the world around us. In recent years, growing awareness of the extent of this impact has triggered an environmental awakening in consumers and businesses alike. Campaigns have been launched and corporate priorities adjusted in order to align behaviours and models with a more sustainable future.

For the pharmaceutical industry, where the ultimate goal is to improve health outcomes, an increasing emphasis is being placed on adapting existing approaches and

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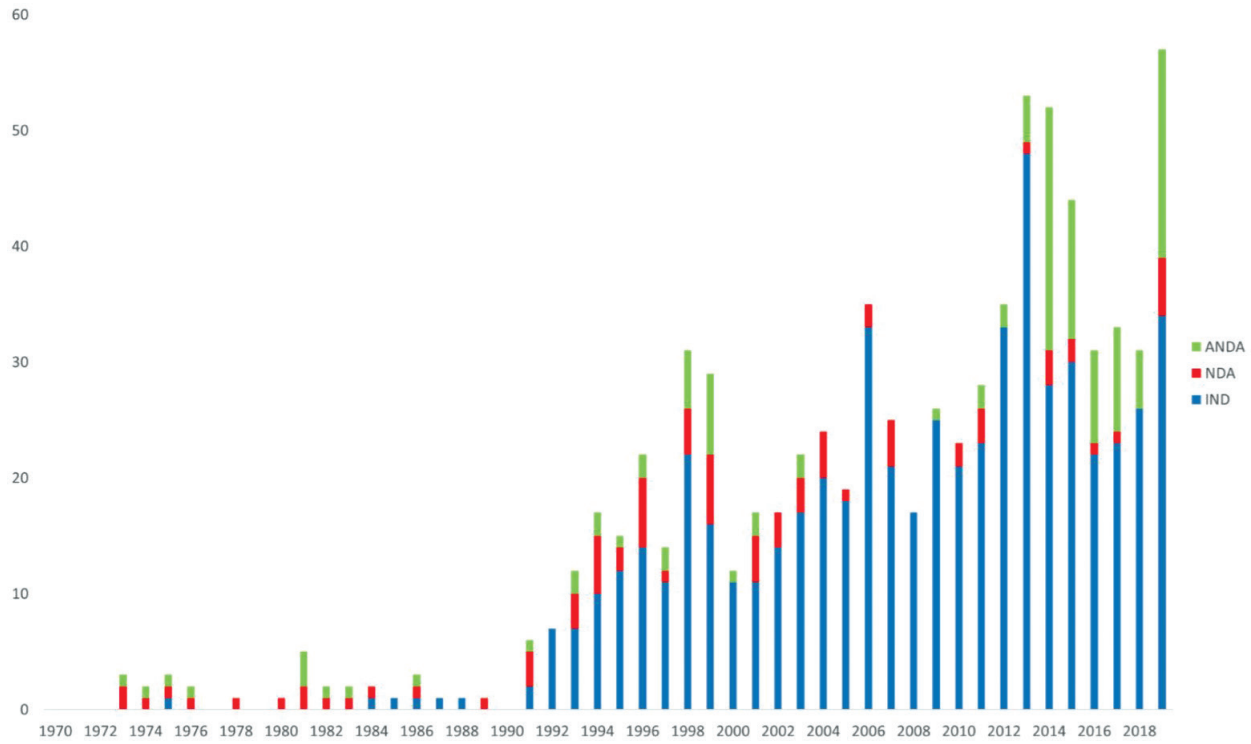

Figure 1: Human drug product submissions to FDA containing nanomaterials between 1970 and 2019.

adopting new ones that give consideration to the ongoing welfare of our planet. These efforts to support sustainability and limit environmental impact are being felt across the entire supply chain. Major pharmaceutical companies have publicly committed to achieve carbon reduction goals and, in some cases, even carbon neutrality as part of ambitious corporate social responsibility programmes.

It is a difficult yet important challenge, but one that the industry can meet by embedding sustainable thinking across all operations, from IT and finance through to R&D and manufacturing. Indeed, drug development, the cornerstone of activity among pharmaceutical companies, is another business area that will need to be carried out with growing consideration for aspects such as energy consumption, materials wastage and the potential for causing pollution.

THE RESURGENT ROLE OF NANOTECHNOLOGY

Drug development, for a significant number of pharmaceutical companies in today's market, is an area increasingly focused on the benefits of nanotechnology, whether for new chemical entities (NCEs) or in the repurposing of existing APIs. Since 1970, the Center for Drug Evaluation and Research (CDER) within the US FDA has received more than 600 submissions of human drug products containing nanomaterials. Furthermore, as shown by Figure 1, half of all of those were submitted within the last ten years, reflecting the acceleration in nanotechnology's growth since the turn of the millennium.[1]

One of the main reasons that nanotechnology has attracted ever greater levels of attention is its strengths in addressing the issues of solubility and stability. Oral administration methods continue to offer high levels of convenience to patients and generally support high levels of compliance. As such, oral remains the preferred administration method for drug formulations, accounting for 62% of all FDA-approved pharmaceutical products.[2] Drugs administered in this way achieve the required level of bioavailability by demonstrating sufficient levels of aqueous solubility to be dissolved in the gastro-intestinal tract.

But while this quality is highly prized, for many it remains just out of reach. An estimated 80% of APIs currently under development suffer from poor aqueous solubility, with high lipophilicity ("grease balls") or high hydrophobicity ("brick dust") commonly cited as reasons for abandoning formulations that may otherwise show promise in addressing unmet medical needs.

While a degree of lipophilicity is required to penetrate the membrane, high levels mean that the molecule may remain inside the membrane rather than passing through. Molecules must also be in solution and in a neutral state for diffusion across the cell membrane to be successful. Whilst nanotechnology cannot change the intrinsic properties of a molecule, it can provide a novel route to overcoming the solubility challenge. At the scale of nano, molecules possess a superior surface area to volume ratio and, therefore, solubility characteristics and dissolution rates are improved.

Further to its benefits in oral administration methods, nanotechnology's strengths are also being exploited for parenteral administration driven by a combination of NCE development, mRNA

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and repurposing for covid-19 solutions. Over the last decade, its use has evolved from simple solutions to facilitating the development of more complex offerings in terms of both solubility and stability.

A DECADE OF PROGRESS AND INNOVATION

These qualities mean nanotechnology has become an area of great importance to pharmaceutical companies and their drug development programmes. Indeed, the potential to improve the chance of success in the development of NCEs addresses one of the key areas of risk in the inherently high-risk, high-cost R&D lifecycle. Although pharmaceutical companies typically employ techniques to enhance bioavailability at a later stage in development, its introduction earlier in the process can also bring greater efficiency overall. Importantly, any savings in time, resources and cost also translate into reduced levels of energy consumption.

Clearly, NCEs are far from the only area where nanotechnology can bring benefits. It is also opening new avenues for existing APIs, enabling them to be re-evaluated to explore the possibility of how, at nanoscale, they can address new disease areas or improve delivery. For example, this is of significant interest in the area of generics, where so-called supergenerics are the product of successful efforts to reap new rewards from drugs whose credentials in terms of safety and efficacy are already well established.

In a similar vein, by addressing shortcomings in the area of oral bioavailability, nanotechnology is enabling new life to be breathed into drug candidates that have either been deemed to have failed previously or whose development may have been placed on hold.

A NEW SENSE OF PURPOSE

Repurposing drugs in this way has been brought into sharp focus this year with the outbreak of covid-19. The novel coronavirus has had a devastating effect on populations across the world, and the pharmaceutical industry has urgently accelerated efforts to bring treatments to market. Given the timeframes involved in developing entirely new treatments, repurposing has taken centre stage, providing a model for rapidly reviewing existing drugs with a view to addressing the symptoms caused by covid-19.

Researchers from the University of Cambridge (Cambridge, UK) were among those in the scientific community to advocate investigating the use of known antivirals to mitigate the effects of covid-19 alongside exploratory work to develop a vaccine, suggesting a co-ordinated global approach to examining the spectrum of licensed drugs.[3] An example of this in action is remdesivir (Gilead Sciences, Foster City, CA, US), an antiviral initially targeted at hepatitis C and used to treat Ebola, which has now been given emergency use authorisation by the FDA for all hospitalised coronavirus patients, after having been indicated for only severe cases initially.

Repurposing, then, presents a significant opportunity for both patients and pharmaceutical companies looking to innovate at speed and reduced cost, and nanotechnology has significant potential in

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supporting this approach. However, there is no single, agreed pathway to nano success. There is a broad range of approaches under the wider nanotechnology umbrella, principally separated into top-down and bottom-up methods and carrier technologies, each of which has implications, not only for characterisation and regulatory requirements, but also for cost and energy consumption.

INTENSIVE EFFORTS REQUIRE INTENSIVE ENERGIES

Wet milling or media milling, for example, which are common top-down techniques, employ abrasion to physically erode the API down to nano scale. In such environments, in order to produce molecules that meet the desired tolerances, several operation cycles may need to be completed, each of which may last for several days, resulting in the need for large amounts of energy to be consumed in the process. It is estimated that particle-size reduction accounts for as little as 2% of the energy consumed during the milling process, with the remainder spent on deformation of particles, inter-particulate and particle-machine friction, heat, sound and vibration.[4]

Another example in the top-down category is high-pressure homogenisation. As the name indicates, this is an energy intensive process, where in the course of milling, the drug particles are exposed to a power density of up to 1013 W/m^3 – a level comparable to power densities observed in nuclear power stations.[4]

Needless to say, the energy requirements, and therefore environmental impact, involved in such approaches is relatively high when compared with bottom-up continuous precipitation methods, which are characterised by higher levels of efficiency. The technology used by leon, for example, enables small molecules, peptides and hormones, including large molecules and high-potency oral and parenteral drugs, to be processed very cost-effectively, without the efforts associated with mechanical intervention. The drug is dissolved in a solvent and then combined with an antisolvent to precipitate stable crystalline or amorphous nanoparticles of uniform size down to 10 nm.

This precipitation method can also be simply and quickly scaled-up from the bench to larger scale, since the nanoparticle production process is identical in the development phase and in commercial production. While it is slightly larger in scale, the footprint of the equipment can be easily integrated into the production facilities of any CMO. This efficient pathway not only means less API is required for screening and validation, it means that decisions about likely success can be made with greater confidence earlier in the process, and the journey to GMP production can be achieved faster, at lower risk and cost and, again, consuming less energy in the process.

The cost-effectiveness of this highly efficient technique is really exposed at the point of scaling to commercial production. While wet milling requires an investment of approximately €20–30 million (£18.4–27.7 million), GMP commercial production equipment based on leon's technology represents an outlay of less than €1.5 million (£1.4 million).

A SINGLE-SOURCE, SUSTAINABLE SOLUTION IS AVAILABLE TO GO, NOW

Underlying this economic argument for creating nanoformulations using bottom-up precipitation techniques is an important environmental argument. From the scalable manufacturing process to the potential for rapidly repurposing existing APIs, efficiency is embedded into the model. Indeed, in the case of leon, this quality is amplified by the company's strong network of alliance partners, which streamlines multi-stakeholder engagement into a unified offering.

All of this means that, along with time and cost, energy consumption and carbon impact are inherently kept to a minimum. It may even extend all the way to the patient, who receives the convenience of orally administered drugs with greater bioavailability at a lower dose, which limits the waste and other complications associated with higher or more frequent dosing and can lead to better compliance outcomes.

Taken together, this shows how, for a pharmaceutical industry with a growing awareness of its responsibilities to the environment, nanotechnology can offer a sustainable pathway for the patient, the patent holder and the planet.

ABOUT THE COMPANY

leon delivers novel, validated and optimised pharmaceutical nanotechnology solutions that create value for clients and provide better outcomes for their patients. It enhances APIs to deliver greater bioavailability, increased solubility and improved stability, revitalising forgotten formulations, and breathing new life into generics. leon's proprietary technology platforms offer access to the next generation of SMART nanoparticles and nano-formulated drugs, adding value at every stage of the supply chain, from partners and payers to caregivers and patients.

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ABOUT THE AUTHOR

Andrea Cusack is a high performing, energetic leader, who has over 25 years' experience in the life science sector. Having acquired a novel blend of technical and commercial expertise in global healthcare organisations across the pharma, consumer health, medical device, biotech and life sciences sectors, Mrs Cusack is uniquely positioned to lead leon and its clients into the next stage of development.

Exciting new possibilities exist at the scale of nano. Opportunities to accelerate drug development. Opportunities for collaboration between global pharma, biotech and network partners to amplify the effectiveness of New Chemical Entities, generate novel generics and super generics, revitalize forgotten formulations and negate the attrition of molecules.

That is why at leon, we are enabling nano now. Join us.

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