CPhI

Ingredients and formulation – evolving opportunities and challenges

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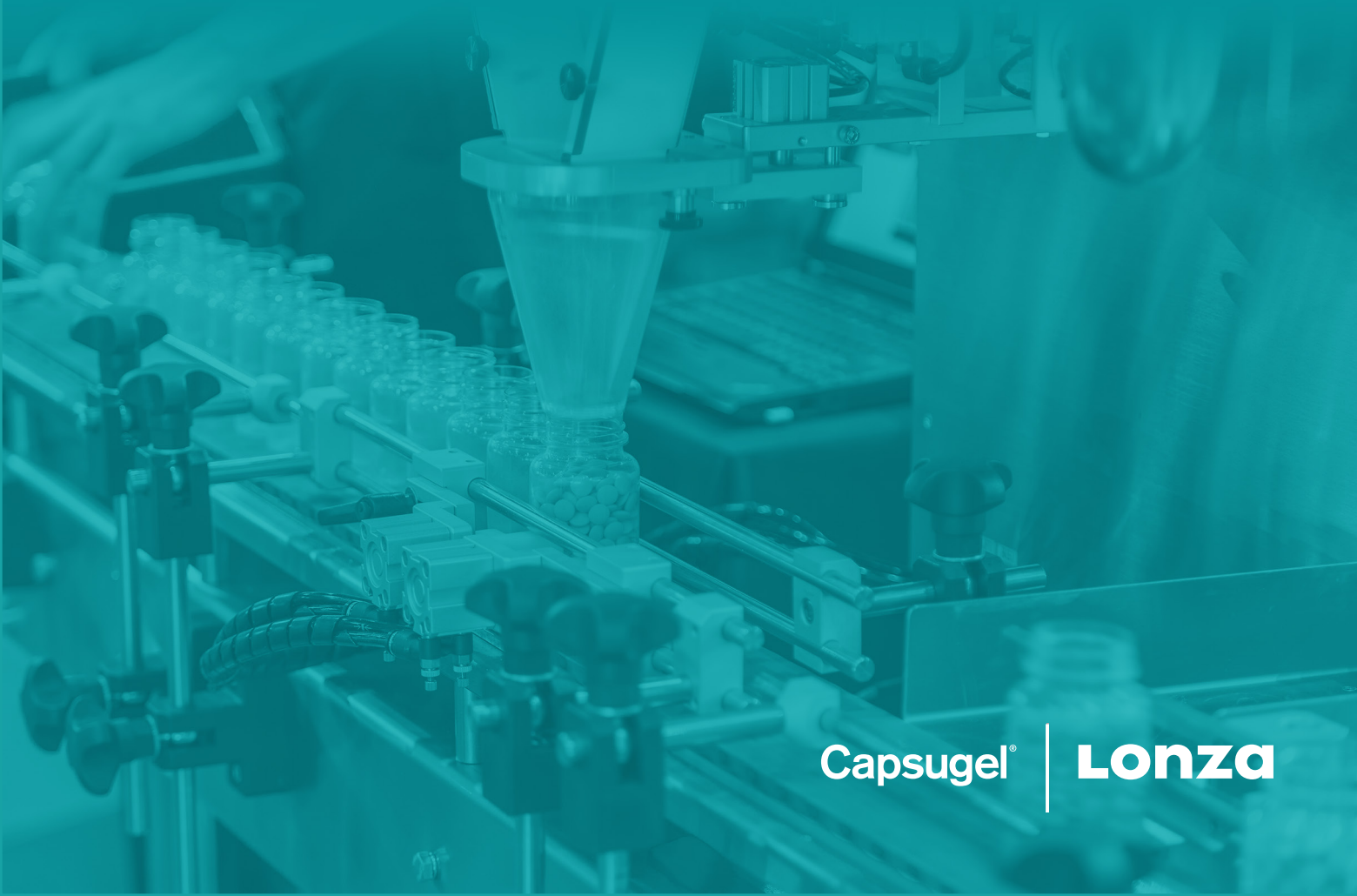
Trend Report 2020



Capsugel® | Lonza

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Foreword

Formulation of ingredients is critical to therapeutic and commercial success

Ingredients are the lifeblood of the pharmaceutical and nutraceutical industries. They connect today's cutting-edge medicine and consumer products makers with their origins in the chemicals sector of the late nineteenth century.

While ingredients play a major part in determining whether a pharmaceutical or nutraceutical product is effective, they do not do it alone. How an ingredient is formulated is critical to the success of a prescription medicine or OTC product, both therapeutically and from a commercial standpoint.

The goal of formulation is to deliver the ingredient to the desired therapeutic target in a manner that ensures therapeutic efficacy and stability, minimizes side effects, does not negatively impact shelf life and is acceptable to the patient or consumer.

Understanding how to formulate an ingredient in the most effective way is the core focus of the pharmaceutical and nutritional sectors and has become an area of convergence for both industries; doing it successfully is a considerable challenge.

And that challenge is becoming ever more difficult. The evolution of drug actives – the increase in complexity and potency for example – has forced industry to develop new dosage forms and ways of using excipients.

Likewise, regulatory demands for safe medicines whose manufacture is better defined is driving ingredients suppliers and formulators to innovate.

Patient and consumer demands are also playing a part. The advent of pharmaceutical consumerism has empowered patients to be more demanding of pharmaceutical and nutritional products.

Patients and consumers want products that are effective, have the lowest possible side effect burden and that are easy and convenient to take. Such demand has prompted efforts to reduce the amount of active pharmaceutical ingredients (APIs) in medicines without impacting efficacy. Again, formulation is playing a key part.

This report looks at how the pharmaceutical and consumer health industries have risen to the challenge of making formulations that comply with evolving efficacy and safety demands while satisfying the needs of patients and consumers.

Ramin Cyrus
Global Head of Marketing
Lonza – Capsules and Health Ingredients

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Section 1:

Active Pharmaceutical Ingredients

A 'global' API market?

The idea of a global API market is something of a misnomer. A huge range and diversity of drug actives are shipped around the world each year, and the suppliers and manufacturers involved can differ for each type.

It is better to visualize the market as being made up of several subsectors, based on the type of API. For example, the small molecule sector includes ingredients made using traditional chemical synthesis processes. Such products are often described as bulk drug products because they are manufactured and sold in large quantities.

High potency APIs is a fast-growing subsector. These ingredients – as the name suggests – are highly potent, which means they are required in relatively smaller quantities than other small molecule APIs. However, HPAPIs are more complex and costly to produce, primarily because facilities making them need enhanced containment and handling systems.

Biotech APIs, in contrast, are those manufactured using living organisms – bacteria or cell lines. These so-called large molecule APIs are usually higher value, low volume products.

API manufacturing

API manufacturing is an equally diverse and fragmented eco-system. While API production facilities are located all over the world, China is widely credited as the largest supplier. According to the UK Medicines and Healthcare Products Regulatory Agency (MHRA)[i], Chinese manufacturers churn out around 40% of all APIs used worldwide.

China's key role in global API supply chains has been acknowledged by Janet Woodcock, Director of the US Center for Drug Evaluation and Research (CDER) who said the country – along with India – supplies many of the ingredients used in pharmaceuticals sold in the US[ii].

Woodcock cited "lower electricity, coal, and water costs" as well as lower environmental standards as important advantages for China's API sector. She also said Chinese API firms are "embedded in a network of raw materials and intermediary suppliers, and so have lower shipping and transaction costs for raw materials."

Even before the COVID-19 pandemic, governments have considered the global pharmaceutical sector's overreliance on APIs made in China as a growing concern.

In August 2019[iii], the Pentagon called US reliance on Chinese actives a security threat prompting government efforts to encourage local production and call for pharmaceutical firms to source APIs from countries other than China.

The calls are in line with comments European and US API industry groups have been making. In January,[iv] the European Fine Chemicals Group (EFCG) – a unit of Europe's chemicals trade body CEFIC that deals with fine chemi-cals – cited Chinese dominance as a supply chain security threat.

The EFCG called for "a 5- to 10-year investment plan to bring critical off-shore technology back to Europe and develop Research and Development into critical raw materials or technologies produced in Europe. These measures will help reduce the EU's dependency on overseas supplies."

API innovation

To compete with China's lower cost base/high-volume production model, API manufacturers in Europe and the US have focused on higher value, often higher potency ingredients.

Analysis by GBI Research[v] suggests 80% of the HPAPIs used worldwide are made in Europe or the US, although China and India are making inroads.

Although there is no fixed definition, HPAPIs are those that have an occupational

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Active Pharmaceutical Ingredients

exposure limit at or below 10 micrograms per cubic meter of air. They target the disease more precisely and selectively than other APIs and are therefore effective at much smaller dosages.

In general, facilities handling HPAPIs require specialist containment technologies to protect employees from accidental exposure and to reduce the risk of cross contamination.

Furthermore, dealing with the minute quantities of ingredient required has forced industry to develop – or invest – in microgram-scale processing technologies.

But the most significant impact HPAPIs have had on formulation development has been financial, according to Paul Cummings from PJC Pharma Consulting. "To date, most companies take a very traditional view on formulation development; bios and highly potent ingredients do pose some challenges, but many of these are already factored into traditional development activities," he says.

"It does factor into the generation of QTPPs[vi] [quality target product profiles] and the acceptable ranges of cost of goods. Novel containment approaches have been deve-loped in some instances, particularly in powder handling."

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(1) Bagchi D, Misner B, Bagchi M, et al. Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. Int J Clin Pharmacol Res. 2002;22(3-4):101-10

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For more information, please contact us at UC-II@lonza.com

Case Study

Lonza's UC-II® undenatured type II collagen – Capsule and Health Ingredients Technology Driving Innovation

Joint Health: consumer demand profile
At every stage of life, consumers are increasingly trying to preserve their mobility, either through sport or physical activities. Unfortunately, active lifestyles can sometimes come at a price: bones and joints – as well as the muscles, tendons, cartilage, and ligaments that help move them – are vulnerable to injury and disease.

According to a 2014 report by the Bone and Joint Initiative (1), musculoskeletal conditions are the most commonly reported medical conditions among people under the age of 65 and the second among those over 65, with only circulatory problems being reported more frequently in the latter group.

While "arthritis" is commonly used to refer to joint pain or joint disease, there are more than 100 types of arthritis and related conditions. People of all ages, sexes and races can and do have arthritis, and it is the leading cause of disability in the US.

There is a wide range of consumers with different needs and concerns to address; whether it is younger athletes practicing activities where the joints are subjected to the shock of impact, young active seniors in the 50-65 age range wanting to preserve their bone capital, flexibility and joint well-being or older seniors, wishing to maintain their mobility, all are seeking potential solutions albeit in varying degrees.

While all these consumer age groups have mobility concerns, the average Millennial (26-39 years old) is less concerned about their musculoskeletal system. So-called Generation X (40-55) and Boomer (56-75) age groups are much more likely to buy joint/bone health solutions. Within these two groupings, so-called 'active silver ager' consumers who want to keep their mobility and continue to perform are driving high demand for solutions.

"In our changing society joint mobility is key and the demand of the ageing population will only continue to grow," - Stephane Vouche, Global Lead Product Marketing, Lonza Consumer Health & Nutrition

Current options for managing osteoarthritis
Due to the high, multi-directional loads placed on joints and repetitive trauma, athletes often begin to suffer from arthritis in important weight-bearing joints at a comparatively early age. Since no cartilage-healing substance has yet been found, hyaluronic acid injections sometimes in combination with local anaesthetics (who can lead to damage of cartilage cells) are still highly valued in the management of cartilage lesions.

When it comes to arthritis pain management, nonsteroidal anti-inflammatory drugs (NSAIDs) are a popular treatment, despite the known adverse effects in the gastrointestinal tract, as well as on renal function. What is often forgotten in daily routine is the considerable hypertensive effect of NSAIDs in everyday life. Moreover, cardiac mortality and myocardial infarction rates are significantly higher under NSAIDs, as sometimes becomes apparent even after just a few weeks of use.[2]

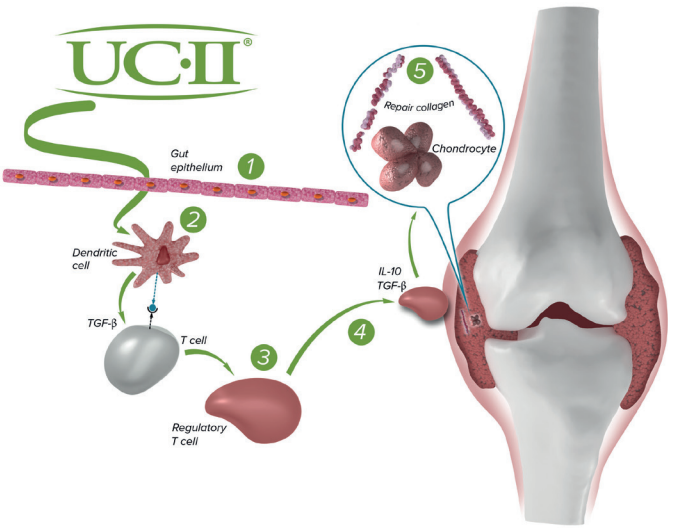

Image: Unique mode of action of UC-II®

UC-II® – an alternative supplement
UC-II® (undenatured type II collagen) is harvested from chicken sternum using a special patented low-temperature, non-enzymatic manufacturing process to preserve the efficacy of its critical undenatured form and is marketed in different oral pharmaceutical dosage forms.

Its mechanism of action is interesting as it does not involve high concentrations of a substance that is a structural component of cartilage being present in the joints on oral intake.

Case Study Continued from page 7

Lonza's UC-II® undenatured type II collagen – Capsule and Health Ingredients Technology Driving Innovation

The effect is thought to arise through the development of oral tolerance due to an interaction between the UC-II® ingredient and the immune cells in Peyer's patches in the small intestine. The regulator T-cells formed during this interaction can produce anti-inflammatory cytokines in the joints, which in turn can have a symptom -modulating and repair effect on the joints.

Several clinical trials have demonstrated that UC-II® supplementation offers joint health benefits not only for people with osteoarthritis, but also for healthy adults. In 2002, Bagchi et al successfully showed that women with joint-health problems were able to achieve clinically meaningful joint-health benefits with UC-II® supplementation after 42 days in a small pilot study with no placebo.[3] Subsequently, two clinical trials (Crowley et al and Lugo et al) confirmed similar benefits in people with knee OA. In these controlled trials, UC-II® supplementation was statistically significantly more effective than glucosamine + chondroitin as measured by WOMAC.[4] In a third randomized placebo-controlled clinical trial (Lugo et al), UC-II® supplementation was found to significantly improve post-exercise recovery, when compared to baseline, in healthy adults who experience joint pain after climbing steps. Overall, UC-II® supplementation was well tolerated with an effective daily dose of 40 mg.[5]

Image: Size 3 Vcaps® Plus capsule containing UC-II

Dosage form development
The performance and consumer appeal of the UC-II® product can be further optimised through the choice of delivery system. In a Lonza survey of silver agers about their dosage form preference, 57% said they preferred the capsule over tablets, liquid form and sachets.[6]

Capsules are a preferred dosage form for the UC-II® ingredient, due to some key advantages, particularly around user compliance. They enable the safe and secure containment and preservation of the undenatured type II collagen — in addition to their taste-masking properties and being easier for consumers to swallow.

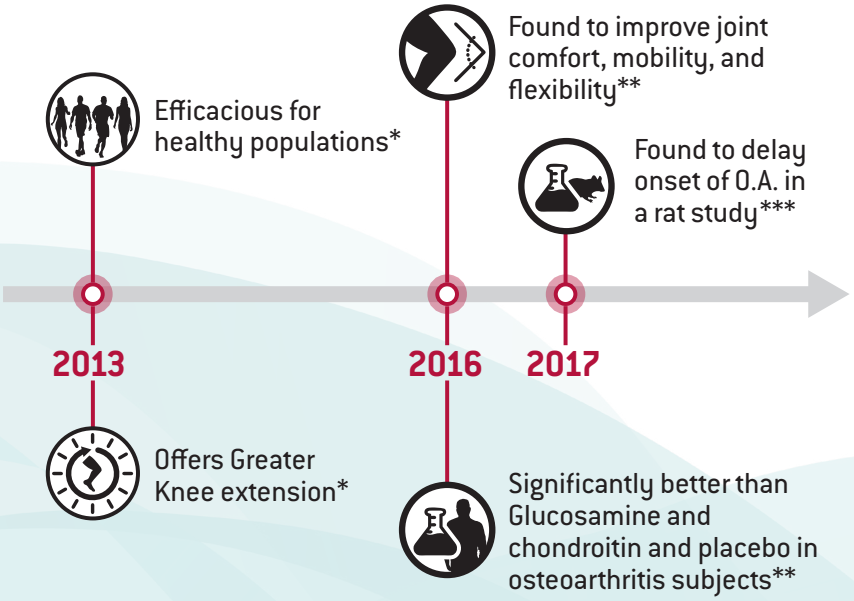

Image: UC-II® clinical studies overview

* Lugo JP, et al. J Int Soc Sports Nutr. 2013;10:48. Bagi CM, et al. Osteoarthritis Cartilage. 2017;25:2080.
** Lugo JP, et al. Nutr J. 2016;15:14. Bagi CM, et al. Osteoarthritis Cartilage. 2017;25:2080.

Case Study Continued from page 8

Lonza's UC-II® undenatured type II collagen – Capsule and Health Ingredients Technology Driving Innovation

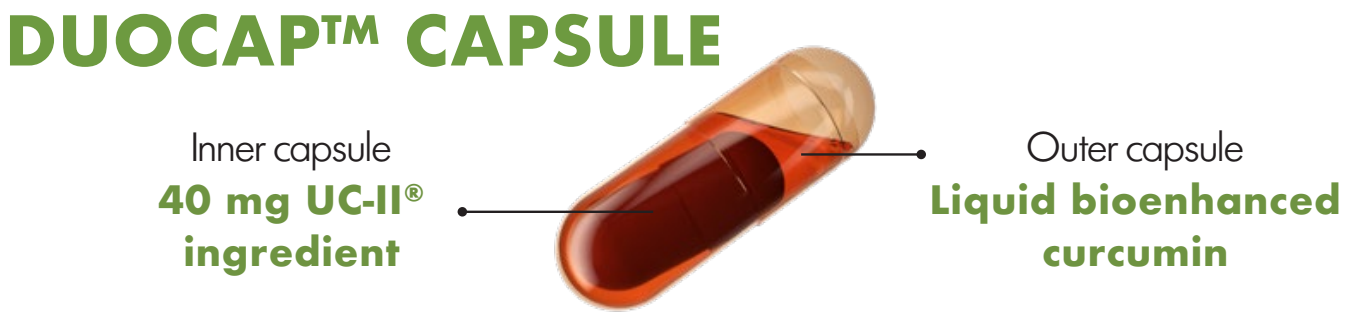

Image : DUOCAP® UC-II® Curcumin Active capsule

For example, Lonza's next-generation Capsugel® Vcaps® Plus capsules can be used to deliver the recommended 40 mg daily dose in a convenient and small size 3 capsule.

Thanks to advances in dosage form technologies at Lonza, it is now also possible to combine the UC-II® ingredient with other trending ingredients in the joint health space, including highly bioavailable curcumin formulations.

For example, with Lonza's Capsugel® DUOCAP® capsule-in-capsule technology, a small dose of the UC-II® ingredient is contained in the inner capsule whereas the curcumin, equal to multiple intakes of a standard dose of curcumin, is delivered in the outer capsule. This enables individuals to benefit from two ingredients in a single capsule, further boosting product appeal in the eyes of the consumer searching for innovation in the joint health space. Vitamin C – which contributes to normal collagen formation for the normal function of cartilage -- can also be delivered alongside UC-II® supplementation in Lonza's Vcaps® Plus capsules.

"The science behind UC-II, the small dosage and the consumer convenience of the final capsule-based product offers new perspectives for the joint health market," – Stephane Vouche, Global Lead Product Marketing, Lonza Consumer Health & Nutrition

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(6) NMI SORD Consumer Study Germany, Italy, France 2017

Section 2

Formulation development

Innovations in APIs prompt invention in the formulation space. Even the most promising candidate compound cannot successfully navigate clinical development and become a commercial success if the formulation is incorrect.

Indeed, most of the compounds identified as having the potential to become APIs in the discovery lab fail during preclinical or clinical development. High attrition rates have been a major headache for the pharmaceutical sector for the past decade, primarily because – even in early phase development – each candidate API has already cost millions to develop.

Bioavailability

Drug candidates fail for a wide variety of reasons, of which one of the most common is solubility, says Cummings.

"The biggest trends are the formulation of poorly soluble drugs," he says, adding "this is an ever-increasing area for new chemical entities; poor solubility and poor bioavailability lead to challenging drug development."

This view is echoed in a recent study[vii] focused on bioavailability, which said "more than 40% of NCEs fall into Biopharmaceutical Classification System (BCS) class II category having a dissolution rate limited bioavailability. A 50%-attrition rate among drugs in development has been reported to result from poor biopharmaceutical properties, including water insolubility."

Industry has responded by trying to develop formulations in which the bioavailability of poorly soluble APIs is improved. Salt formation, use of cyclodextrins and the production of nano-suspensions have emerged as leading solubility enhancement methods[viii].

Other methods such as the use of emulsions or surfactants have also entered the field of formulation development.

Permeability

Solubility enhancement is not the only need driving innovation in the formulation space. Permeability – the ability to pass through membranes like the gastrointestinal tract – is also an issue for a significant number of APIs.

Industry efforts to boost permeability have focused mainly on the use of chemicals that ease paracellular passage – movement through the intracellular space – and increase transcellular absorption. A huge and highly diverse range of chemicals are employed.

Examples of permeability enhancers include detergents, surfactants, bile salts, chelating agents, fatty acids, medium chain glycerides, acyl carnitine, alkanoyl cholines, N-acetylated a-amino acids, N-acetylated non-a-amino acids, chitosans, mucoadhesive polymers and phospholipids.

Metabolism

All drugs – and the APIs they contain – are metabolised prior to excretion in two stages. Firstly, the APIs are degraded as a result of chemical reactions, typically hydroxylation and oxidation. Secondly, so-called derivatization reactions occur – those that break down the compound into derivatives for excretion.

The challenge for formulators is to try and protect the ingredient for long enough to allow it to have the desired therapeutic effect. Most such efforts are based on the use of excipients that slow the breakdown of APIs. Chemicals such as Tween 80, Cremophore EL and Solutol HS have been shown[ix] to have such an impact.

However, surfactants like those mentioned above can be problematic in clinical use. Some have been shown[x] to induce hypersensitivity reactions when present in formulations used in clinical trials.

Section 2 Continued from page 10

Formulation development

As a result, several other approaches are also used to prevent APIs being metabolized too quickly. Foremost among these is the attachment of a polymer to stabilize the ingredient in question. The idea is that the polymer shields the API against enzymes and chemicals that would otherwise result in its rapid degradation and elimination.

Polymers including various dextrans, polyethylene glycol (PEGs), N-(2-hydroxypropyl) methacrylamide (HPMA) and polyglutamic acid are being assessed in the clinic.

Modified release

Recent decades have seen the concept of a modified release (MR) formulation being firmly embraced by the pharmaceutical industry. The idea, as the name suggests, is to create a formulation that releases the API at a specific local or time point.

There are multiple potential advantages. For example, ensuring an API is released near its target rather than systemically accelerates the onset of action and can increase therapeutic efficacy. The approach also minimizes the risk of off-site side effects and – in the case of injectable depot formulations – reduces the number of administrations required.

From a commercial standpoint, modified release formulations also allow pharmaceutical companies to extend the life cycle of their products by letting them patent and launch MR versions of drugs as they come off patent.

Biologics formulation

Biologic APIs are another major driver of innovation in formulation development. In addition to some of the issues mentioned above, biological ingredients present additional challenges, many of which are related to their susceptibility.

Unlike small molecule APIs that degrade as a result of chemical interactions, the therapeutic activity of biological ingredients can be impacted by environmental changes that alter their structure.

To address such issues, formulators have focused on stabilizing biological APIs – primarily proteins and peptides – using treatments. For example, removal of liquid via processes such as lyophilisation has been shown to increase stability.

One important caveat is that freeze-drying is not suitable for all biologic APIs. In some it has been shown[xi] to induce "cold denaturation." To address this, formulators use cryo-protective compounds – sugars like mannitol, trehelose, maltose and fructose – to offset the negative impact of lyophilisation. Sugars have also demonstrated the ability to reduce aggregation of protein APIs by minimizing thermodynamic activity. Surfactants[xii] have also been used for this purpose, as have certain salts and buffering agents.

Chelating agents like edetic acid (EDTA) and Tris (tromethamine) are also used to stabilize protein APIs and to protect them against degradation[xiii].

Injection alternatives

The vast majority of biopharmaceutical APIs are formulated in solution for injection. However, for the reasons mentioned above, as well as patient aversion to injections, efforts to develop alternative oral formulations are ongoing.

"There is a constant stream of research in these areas; liquids are the current gold standard and also the simplest to generate and control but research is underway prototyping alternatives, as yet the majority of these have yet to reach the clinic," says Cummings.

This view is shared by Molly Strausbaugh, Assistant Director focusing on formulations science at CAS, a division of the American Chemical Society: "The growing importance of biologics, including cell and gene therapies, is also driving innovation in the formulations space.

"Traditionally, these types of therapies have been liquid injectables – but for cost

Section 2 Continued from page 11

Formulation development

and compliance reasons there is lots of research on alternative dosage forms and approaches including enteric coatings, combination therapies, increasing stability, and changing pharmacokinetic properties of the formulation."

A similar point was made by a study[xiv] published in the journal *Pharmaceutical Technology and Development*.

The authors wrote: "To achieve an efficient delivery of such molecules by non-parenteral route, in particular, via the oral route, novel concepts are needed not only to overcome significant enzymatic and diffusion barriers but also to ensure stability and biological activity" – with alternative formulations identified as the most likely solution.

Therapeutic efficacy

In addition to preventing degradation, formulation is also used to improve the therapeutic efficacy of biologic APIs.

Here the aim is to prevent APIs being broken down by immunological responses – digestion by naturally occurring proteolytic enzymes[xv] for example. Again, polymer conjugation has become a popular strategy, with the addition of polyethylene glycol being one of the most common approaches.

Encapsulation is also used to enhance the therapeutic activity of biologic APIs. Liposomes and nanoparticles that precisely control API release have been developed[xvii].

Patient compliance

Increasing patient compliance is another area of focus in the healthcare industry where the work of formulators is having an important impact.

Strausbaugh says that changing the physical form of a medication can be a key step to increasing patient compliance by overcoming identified barriers to adhering to a treatment regimen.

"As physicians want to increase patient compliance, they may select medications to prescribe based on this driving market share shifts," she adds.

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Section 3:

Manufacturing Techniques

Formulation can help turn a promising API into an effective drug. But for the drug to become a commercially successful product requires that the formulation be manufactured in a cost-effective manner.

As a result, innovation in the formulation space has prompted innovation in manufacturing with various methods and production technologies being used to make pharmaceuticals.

Hot melt extrusion (HME) involves heating a polymer and forcing it through an extruder. The method, which was developed in the 1930s, is used to make uniform polymers in which constituents are evenly distributed.

HME was initially used in the plastics and food sector. However, in recent years[xviii] it has been employed in pharmaceutical production, particularly for the manufacture of drugs that contain poorly soluble APIs. Advantages of the approach include the ability to use a wide range of excipients and the ease with which process analytical technology can be incorporated.

In a similar way, **spray drying** has become an increasingly popular technique in the production of formulations of poorly soluble APIs. In spray drying a liquid formulation is sprayed onto a surface and allowed to dry to produce a powder.

In pharmaceutical manufacturing, spray drying is suited to the production of peptides, proteins or poorly water-soluble APIs, particularly antibiotics[xix], because it allows them to be co-processed with solubility enhancement excipients. Another advantage is that the approach reduces the number of unit operations, potentially lowering manufacturing costs.

More recently, **micronization** – the formation of an API into ultrafine, precise particles – has been embraced by the pharmaceutical manufacturing industry. The method[xx] – which is related to spray drying – involves processing the API in question into a particle usually less than 10 µ in diameter.

The aim[xxi] is to enhance the bioavailability of poorly soluble APIs - in particular those belonging to BCS class II or class IV – by increasing particle surface area.

Section 4:

Regulation

API producers need to meet the regulatory requirements in the countries they supply. In the US, EU and other major markets, APIs need to be made in accordance with current good manufacturing practices (cGMP) modelled on ICH Q7A.[xxi]

While there are subtle differences depending on the region, in general cGMP guidelines set out quality and purity expectations for APIs used in that market.

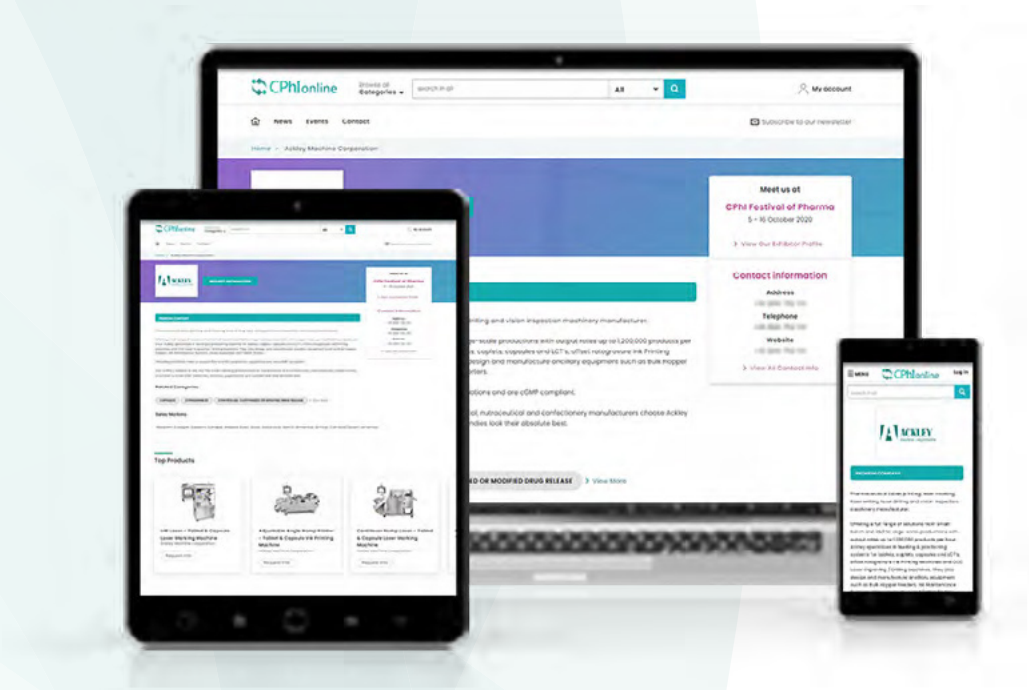
cGMP principals are well established and have been relatively stable for decades. Recent updates have focused on mitigation of supply chain issues caused by the coronavirus pandemic.

On June 19, 2020[xxiii], for example, the US Food and Drug Administration (FDA) issued guidelines designed to advise API firms how to prevent products being contaminated by SARS-CoV-2, the causative agent of COVID-19. It also explained how to ensure continuity of manufacturing operations.The regulation of formulations is more complex. Finished drug formulations – including the APIs, excipients and other materials they contain – must be made in compliance with cGMP and more generalized guidance on product development†[xxiv].

However, as each pharmaceutical formulation is a separate product, each is approved as a separate entity.

The added complexity is that regulatory agencies issue guidance documents for certain product types.

Opioid-containing pain medicines are one such example. The past decade[xxv] has seen a dramatic increase in opioid abuse in the US. As part of a wider effort to address the epidemic, the FDA issued guidelines[xxvi] for opioid painkiller formulators, requiring that they include abuse deterrent technologies.



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Section 5:

Future formulations and cost reduction

In the future, techniques such as additive manufacturing – also known as 3D printing – are likely to play a greater role in formulation production.

In 2015[xxvii] the FDA approved Spritam, an epilepsy drug made using 3D printing. The drug is a formulation of levetiracetam that is printed into a porous formulation which rapidly disintegrates in liquid.

The agency's chief at the time, Scott Gottlieb, predicted[xxviii] the product would be the "tip of the iceberg given the exponential growth of innovative research in this field."

He also said the FDA plans to support industry adoption of 3D printing and other innovative dosage form manufacturing techniques, citing the CDER's Emerging Technology Program as an example of its approach.

The Programme provides opportunities for early engagement regarding innovative approaches to product design or manufacturing. The FDA lists ultra-long acting formulations as one of the areas in which it is already working with developers.

For Strausbaugh, cost reduction will also drive innovation in formulation development.

"There is increasing focus on reducing the cost of healthcare overall, and this is putting increased pressure on the pharmaceutical industry to reduce the cost of medications," she says. "Innovations in the formulations phase of drug development and reformulating existing pharmaceuticals are playing an important part in contributing to that goal by, for example, finding alternative excipients that are less expensive but are still safe and don't interfere with performance."

She adds that formulating medications into different physical forms is also contributing to cost reduction because oral medications, for example, are typically less expensive for a consumer than an injectable.

"Thus, these formulations innovations can provide competitive advantages for a pharmaceutical company in the competitive managed healthcare environment," she says.

Conclusions:

The challenges of bringing a pharmaceutical or consumer health product to market are manifold. One could be forgiven for assuming that the lion's share of the hard graft and application of scientific knowledge comes at the drug discovery stage when promising candidates are identified. However, in truth, it is but the first step on a long ladder to success.

The sheer complexity of pharmaceutical formulation in terms of addressing issues around bioavailability, therapeutic benefits and safety to name but three make it the stage in the development process where raw potential can be truly unlocked.

Pharmaceutical and consumer health manufacturers are constantly having to innovate to overcome shifting and evolving regulatory hurdles and comply with cGMP when formulating, while healthcare budget limitations in many countries mean they increasingly need to take cost reduction into consideration.

New manufacturing processes and technologies could go a long way to enhancing pharmaceutical formulation, but in the future, if the pharmaceutical industry is to continue to ensure effective medicines reach patients, it will have to continue to do in this crucial stage what it does in other stages of the product lifecycle: drive innovation.

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