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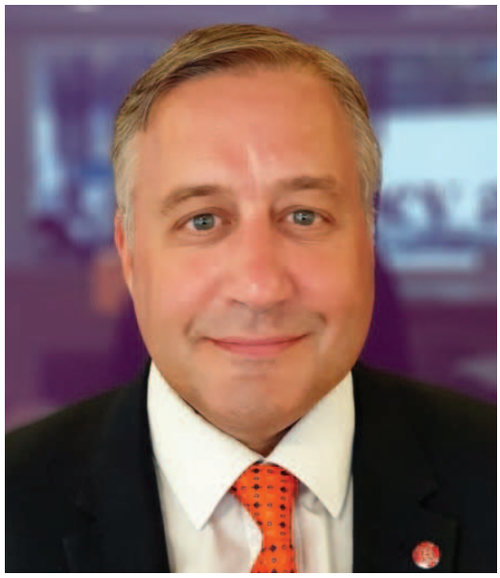
editorial

Dear Colleagues



I am pleased to introduce the second issue of the revamped IP Journal which the Precision Health Technologies Accelerator (PHTA) is proud to sponsor and support. As usual we have an eclectic mixture of articles which reflect the multi-disciplinary field of Industrial Pharmacy. We start off with the latest observations in the use of Medicinal Cannabis which is still being characterised therapeutically and then follow this with a look at Continuous Manufacturing and its advantages over the more traditional approach of batch production.

Our third article emphasises the importance of water in the production of pharmaceuticals and its influence on product quality, but this can only be ensured by reducing the bioburden in water systems. Our final article is titled Risk Review and Monitoring and is a sample chapter from a recent EC/PDA book on Quality Risk Management. We then complete this issue with another thought-provoking article in our popular Bottled Brown series.

Our aim is to spread and share knowledge and in so doing encourage innovation – and innovation can only occur if knowledge and ideas are freely exchanged.

I remember the Lost at Sea exercise developed by the US Coast Guard at the INSEAD technology programme which had a profound effect upon my psyche. In this exercise you are asked as individuals to select in priority order 15 items as you are abandoning a sinking ship and climbing into a life raft. You are then asked to repeat this exercise in various groups and the results are analysed. Not to spoil the ending for you – but over the last 25 years the answer has always been the same – multi-disciplinary project teams always perform better during this exercise in comparison to conducting the exercise as individuals.

By providing such a variety of articles I also want to encourage possible serendipity where you may read the journal for a particular topic and suddenly you find another article or reference which may help you find a solution to a problem you have been working upon – a phenomenon which has happened so many times in my career.

As always, if you would like to submit an article or letter please feel free to reach out to us – we would be delighted to accommodate you.

All that remains for me is to wish you a wonderful and relaxing summer.

Best regards

Professor Gino Martini FRPharmS
Editor, *Industrial Pharmacy*

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We hope you enjoy* Industrial Pharmacy *and find it both useful and informative. We are currently seeking new articles for future issues of the journal and would like to invite you to contribute an article or review paper on any aspect of* industrial pharmacy *to the journal. We are also pleased to receive letters on any aspect of pharmacy or with respect to any article published in the journal. All issues of* Industrial Pharmacy *are indexed by both Scopus and Embase and thus are available through the listings for all other scientists internationally.

Cannabis Based Medicinal Products - a novel approach in the Management of Front-Line Mental Health Conditions

by Anup Mathew and Tim Henley

This article explores Cannabis-Based Products for Medicinal Use (CBPMs) and their potential to revolutionise personalised health care. These new drugs offer novel approaches to managing frontline mental health conditions. Despite past biases, new research highlights cannabis's rich pharmacological profile, including cannabinoids like THC and CBD, which interact with the body's endocannabinoid system (ECS). The ECS modulates stress responses, emotional regulation, and neuroinflammation, making cannabinoids promising therapeutic agents for conditions such as depression and anxiety.

Professor Anup Mathew is the Medical Director for Lumir Clinic which is the only research-based Medical Cannabis clinic in the UK and based in the PHTA building in Birmingham. He is also a senior NHS Consultant Psychiatrist and one of the most experienced and respected clinicians working in the Medical Cannabis field, reflected in his role as a trainer for new prescribers in the UK and abroad. Professor Mathew has a special interest in military psychiatry reflected by his role as a Royal Navy Reserve Medical Officer.

Tim Henley is the UK Director of Lumir Clinic. Tim has extensive expertise in cannabis industry and technology-driven solutions. Since 2017, he has played a pivotal role in the UK industry helping form one of the UK's first industry trade bodies. He has worked for several significant international companies in the sector using his personal experience to drive his advocacy of Medical Cannabis as novel treatments and driving research. His leadership has fostered ground-breaking research partnerships, including collaborations with several Universities.

Introduction

In 2023 alone, suicide was the acknowledged cause of 6,069 registered deaths in the UK – over 16 people dying daily – with 75% being men[1]. These shocking statistics highlight why novel approaches to treatment are critical to stemming the rising mental health crises affecting all walks of life and ages across the UK. Cannabis based treatment now offer such a novel approach to the management of these conditions.

Medical cannabis, unfortunately, has a continuing image issue due to chronic cannabis abuse driven by the illicit market. The confirmation of bias around illicit cannabis has led to entrenched resistance in the scientific community to its potential as a modern medicine. Dr Lumir Hanus was the discoverer of Anandamide, one the body's endocannabinoids[2,3] and often referred to as the bliss molecule because in part it is responsible for the "runners high" often experienced by athletes and which can also be a factor in helping patients improve their quality of life over time.

Cannabis Based Products for Medicinal use (CBMP'S)

Cannabis as a medicine has been known since ancient times in China. But it was only in the 19th century that cannabis as a medicine was recognised and used in Europe for its analgesic, anticonvulsant, anti-spasmodic, anti-emetic, and hypnotic effects.

The UK government legalised medical access to Cannabis on 1st November 2018. This created a new category of medicines called CBPM's (Cannabis-Based Products for Medicinal Use) which by definition all stem from Cannabis. However, Cannabis is not just one active substance. The myriad of cannabis cultivars are a pharmacological treasure chest of phytocannabinoids, flavonoids and terpenes that all combine, mainly in the trichomes of the unfertilised female flower to give each cultivar a unique profile and highly distinctive smell which some readers will be familiar with.

The Neuromodulating Effects of Cannabinoids

Cannabis contains approximately 400 distinct chemical compounds (phytochemicals), including over 100 cannabinoids, the most prominent being D9-tetrahydrocannabinol (THC) and cannabidiol (CBD)[4]. THC exerts its pharmacological activity mainly by engaging with type-1 and type-2 cannabinoid receptors, namely CB1 and CB2 receptors.These are G protein-coupled receptors that are expressed in numerous cell types throughout the body but differ significantly in their tissue distribution. CB1 receptors are present in large quantities in the central and peripheral nervous system, gastrointestinal tract, skeletal muscle, and adipose tissue, whilst CB2 receptors are mainly found on immune cells, including the glia, where they modulate cytokine release amongst other functions[5]. Cannabinoid receptors are activated by the endogenous cannabinoids (endocannabinoids)

Figure 1. Cannabis flower Trichomes

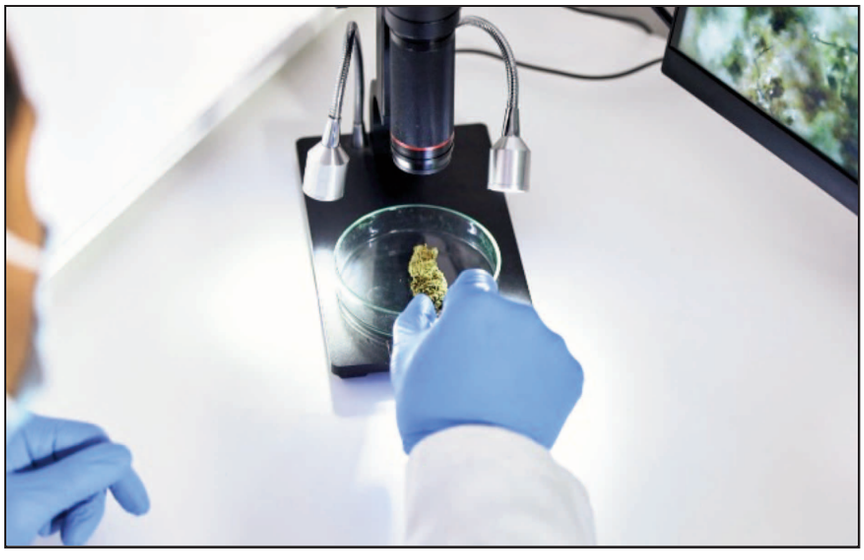

Figure 2. Cannabis sample

arachidonoylethanolamide (anandamide, AEA), and 2-arachidonoylglycerol (2-AG). These are bioactive substances derived from arachidonic acid and produced on demand from membrane phospholipids[6].

The Endocannabinoid System (ECS)

Cannabinoid receptors, endocannabinoids and the enzymes involved in their synthesis and degradation comprise the endocannabinoid system (ECS), a functionally diverse regulator of many physiological processes which favours homeostasis[7]. AEA and 2-AG are synthesised in the postsynaptic neuron, released into the synaptic cleft, and bind as agonists to the presynaptic CB1 receptor located on the axon terminal or the CB2 receptors in glial cells. Via its G-protein coupled mechanism, binding at the CB1 receptor has a resultant effect of attenuating axonal calcium influx[8]. AEA and 2-AG are eventually degraded by hydrolytic enzymes, namely fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (see **Figure 3A**). FAAH is found distributed widely in the CNS and cortex, which is also known to have a high preponderance of CB1 receptors. These enzymes function to regulate and control endocannabinoid signalling by modulating the lifespan of endocannabinoid molecules. From a neurobiological perspective, activation of the CB1 receptor has a multitude of additional effects in the central and peripheral nervous system, the net effect of which is to dampen neuronal excitability and modulate neuro-transmission. Furthermore, there

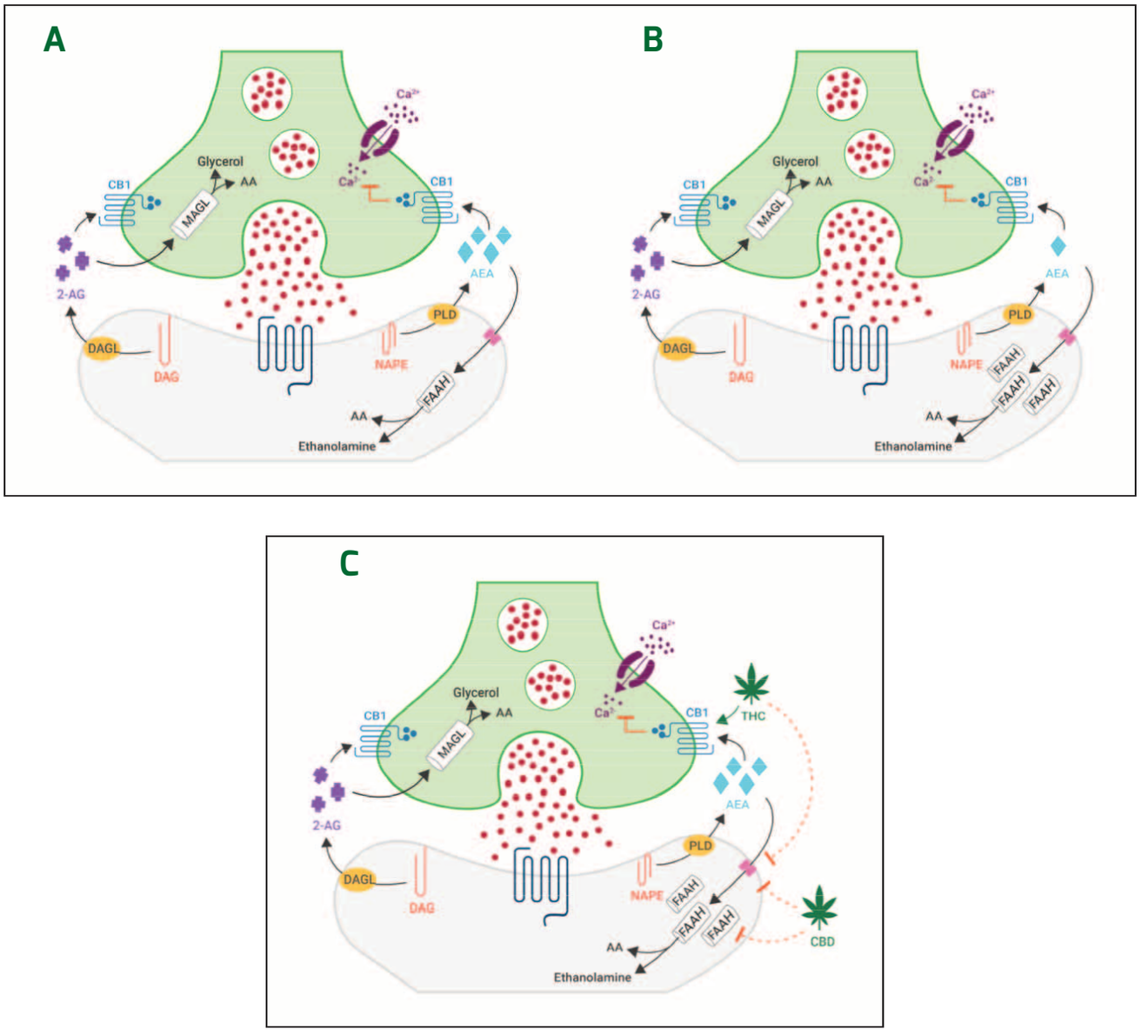

Figure 3. A series of diagrams illustrating the production of endogenous cannabinoids 2-AG and AEA from precursor molecules, their mechanism of action at the presynaptic CB1 receptors (with the resultant effect of reduced presynaptic calcium influx and hence neuronal excitement), and subsequent degradation by FAAH and MAGL. (A) Normal ECS functioning; (B) the ECS in EUPD showing an increase in FAAH-mediated degradation of AEA; (C) potential exogenous cannabinoid mechanism of action at the presynaptic CB1 receptor and at the postsynaptic deactivation of anandamide.

is substantial preclinical evidence of a range of other impacts at a cellular level, which include CB1 receptor-induced inhibition of new synapse formation and the retraction of neurites resulting in neuronal morphological changes[9] and the modulation of microglial cytokine production in murine models of neuroinflammation[10].

The Endocannabinoid System as a Therapeutic Target for Mental Health Conditions

It has been postulated that the ECS plays a significant role in the pathogenesis of many psychiatric conditions. The regions of the brain often implicated in many mental disorders, namely the limbic cortex, prefrontal cortex, amygdala, and hippocampus also contain a high concentration of the ECS. This is a dynamic arrangement that may be influenced by external factors; for example, exposure to chronic stress in mice results in significantly increased CB1 receptor agonist binding site

density in the prefrontal cortex and a decrease in CB1 receptor agonist binding site density in the hippocampus, hypothalamus, and ventral striatum[8]. Hippocampal dysfunction is associated with an increase in circulating glucocorticoids after exposure to chronic stress, which is thought to occur through negative inhibition of the hypothalamic–pituitary axis (HPA). Due to the high density of CB1 cannabinoid receptors in this region, endocannabinoids may have an important role in this negative feedback loop. Several studies have shown that increased cannabinoid hippocampal signalling can prevent stress-induced behavioural changes[11]. Chronic stress is also associated with relevant physiological changes affecting ECS functioning, both within this circuit but also throughout the CNS. Notable findings include reduced AEA, increased 2-AG, loss of CB1 receptors, and increased FAAH levels. The ECS in the prefrontal cortex, amygdala, and hippocampus is responsible for suppressing the activity of the HPA following acute exposure to stress and thereby modulates the stress response through the reduction of circulating glucocorticoids. The consequences, therefore, of a dysfunctional ECS system are a prolongation of the stress response due to reduced negative feedback from the CB1 receptor system[11].

One of the leading hypotheses for the pathogenesis of emotional dysregulation (ED) is an abnormal function of the amygdala–PFC circuit. This circuit is implicated in higher-order decision-making and appropriate fear response, both of which are typically impaired in patients diagnosed with ED. Dysfunction in the PFC may manifest clinically as impaired decision-making or impulsivity and has been noted to be hypo-responsive in functional imaging studies, whereas heightened amygdala response is thought to lead to symptoms of increased negative emotion. The current model, elucidated experimentally by ^{11}C-CURB PET functional imaging, suggests that stress and genetic predisposition may increase the local expression of the endocannabinoid-degrading enzyme FAAH in key regions of this circuit, resulting in lower levels of circulating anandamide and leading to emotional dysregulation[12] (**Figure 3B**). Pharmacological intervention with cannabinoids may help alleviate symptoms of many psychiatric conditions either by directly activating cannabinoid receptors, as is the case with THC, or by restoring endocannabinoid signalling in this crucial circuit. Sustained administration of oral CBD has also been shown to increase circulating levels of anandamide in psychotic patients, which may be achieved by several mechanisms[13] (**Figure 3C**).

An alternative plausible mechanism for the therapeutical action of cannabinoids in ED could be through the control of neuroinflammation, which is increasingly thought to play a key role in the aetiology of several psychiatric disorders including depression, epilepsy, obsessive-compulsive disorder, and schizophrenia[14]. MacDowell *et al.* demonstrated that patients with ED present increased activation of inflammatory pathways and inhibition of the antioxidant pathway with a partial correlation to impulsivity scores[15]. Exogenous cannabinoids have been studied extensively as emerging anti-inflammatory agents, which are proposed to act as immunomodulators via several mechanisms that may or not be mediated by cannabinoid receptors. First, it is well known that both THC and CBD can induce apoptosis in immune cells with significant levels of THC-induced apoptosis observed in T cells, B cells, and macrophages[16]. Cannabinoids can also impart a protective effect from apoptosis in healthy CNS cells with a possible role in autoimmune conditions such as multiple sclerosis[17]. Preclinical studies have demonstrated that 3D mice brain aggregate cell cultures with CB1 receptor knockout showed greater caspase-3 activations and decreased neurofilament-H expression when exposed to IFN-ϒ compared to wild-type cultures, indicating the neuroprotective role elicited through CB1 receptor activation[18]. In addition to this, cannabinoids are also thought to act via the downregulation of cytokine and chemokine production[16]. This situation is further illustrated by evidence that murine astrocytes exposed to bacterial lipopolysaccharide released significantly less nitric oxide when given AEA compared to a CB1 receptor cannabinoid antagonist[19].

Conclusion

There is now acceptance that medical cannabis has demonstrable beneficial therapeutic effects in conditions including chemotherapy-induced nausea and vomiting, chronic pain, multiple sclerosis, anxiety,

sleep disorders and epilepsy, all within a satisfactory safety profile[20]. The neuro- and immune-modulatory effects of THC and CBD seem theoretically well-aligned with cellular and molecular deficits that are currently being investigated as key features underlying the pathogenesis of ED.

References

1. https://www.mind.org.uk/about-us/our-policy-work/reports-and-guides/the-big-mental-health-report-2024/
2. Hanus. LO. Discovery and Isolation of Anandamide and Other Endocannabinoids - Hanuš - 2007 - Chemistry & Biodiversity - Wiley Online Library
3. https://lumirclinic.co.uk/professorlumirhanus/ Why are we named Lumir Clinic? - Lumir
4. Ashton CH. Pharmacology and effects of cannabis: A brief review. *Br. J. Psychiatry*, 2001, 178, 101-106. [CrossRef]
5. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: An overview. *Int. J. Obes*. 2006, 30 (Suppl. 1), S13–S18. [CrossRef]
6. Palmer SL, Thakur GA, Makriyannis A. Cannabinergic ligands. *Chem. Phys. Lipids*, 2002, 121, 3-19. [CrossRef]
7. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. *Nat. Rev. Drug Discov.,* 2004, 3, 771-784. [CrossRef] [PubMed]
8. Hill MN, Carrier EJ, McLaughlin RJ, Morrish AC, Meier SE, Hillard CJ, Gorzalka BB. Regional alterations in the endocannabinoid system in an animal model of depression: Effects of concurrent antidepressant treatment. *J. Neurochem.,* 2008, 106, 2322-2336. [CrossRef] [PubMed]
9. Kano M, Ohno-Shosaku T, Hashimotodani Y, Uchigashima M, Watanabe M. Endocannabinoid-Mediated Control of Synaptic Transmission. *Physiol. Rev.,* 2009, 89, 309-380. [CrossRef] [PubMed]
10. De Meij J, Alfanek Z, Morel L, Decoeur F, Leyrolle Q, Picard K, Carrier M, Aubert A, Séré A, Lucas C, et al. Microglial Cannabinoid Type 1 Receptor Regulates Brain Inflammation in a Sex-Specific Manner. *Cannabis Cannabinoid Res.*, 2021, 6, 488-507. [CrossRef] [PubMed]
11. Morena M, Patel S, Bains J, Hill MN. Neurobiological Interactions between Stress and the Endocannabinoid System. *Neuropsychopharmacology,* 2015, 41, 80-102. [CrossRef]
12. Kolla NJ, Mizrahi R, Karas K, Wang C, Bagby RM, Mc Main S, Simpson AI, Rusjan PM, Tyndale R, Houle S, *et al.* Elevated fatty acid amide hydrolase in the prefrontal cortex of borderline personality disorder: A [11C]CURB positron emission tomography study. *Neuropsychopharmacology*, 2020, 45, 1834-1841. [CrossRef]
13. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl. Psychiatry,* 2012, 2, e94. [CrossRef]
14. Rupprecht R, Rupprecht C, Di Benedetto B, Rammes G. Neuroinflammation and psychiatric disorders: Relevance of C1q, translocator protein (18 kDa) (TSPO), and neurosteroids. *World J. Biol. Psychiatry,* 2021, 1-7. [CrossRef]
15. MacDowell KS, Marsá MD, Buenache E, Villatoro JML, Moreno B, Leza JC, Carrasco JL. Inflammatory and antioxidant pathway dysfunction in borderline personality disorder. *Psychiatry Res.,* 2020, 284, 112782. [CrossRef]
16. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. *Futur. Med. Chem.,* 2009, 1, 1333-1349. [CrossRef]
17. Croxford JL, Pryce G, Jackson SJ, Ledent C, Giovannoni G, Pertwee RG, Yamamura T, Baker D. Cannabinoid-mediated neuroprotection, not immunosuppression, may be more relevant to multiple sclerosis. *J. Neuroimmunol.,* 2008, 193, 120-129. [CrossRef] [PubMed]
18. Jackson SJ, Baker D, Cuzner ML, Diemel LT. Cannabinoid-mediated neuroprotection following interferon-gamma treatment in a three-dimensional mouse brain aggregate cell culture. *Eur. J. Neurosci.,* 2004, 20, 2267-2275. [CrossRef] [PubMed]
19. Molina-Holgado F, Molina-Holgado E, Guaza C, Rothwell NJ. Role of CB1 and CB2 receptors in the inhibitory effects of cannabinoids on lipopolysaccharide-induced nitric oxide release in astrocyte cultures. *J. Neurosci. Res.,* 2002, 67, 829-836. [CrossRef] [PubMed]
20. Nutt D. Why doctors have a moral imperative to prescribe and support medical cannabis—An essay by David Nutt. *BMJ,* 2022, 376, n3114. [CrossRef]

Overview of the Pharmaceutical Industry's Drive Towards Continuous Manufacturing

by Jason Kelly

This article explores the pharmaceutical industry's shift towards Continuous Manufacturing (CM), a modern approach that facilitates uninterrupted production flows compared to traditional batch methods. CM offers numerous advantages, including enhanced product quality through real-time monitoring, improved efficiency, cost reduction, and increased supply chain flexibility. Key technological innovations driving this transition include Process Analytical Technology (PAT), automation, modular production systems, and single-use technologies.

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Introduction

Major pharmaceutical companies, such as Johnson & Johnson, Pfizer, Novartis, and Vertex Pharmaceuticals, are leading the way in CM adoption, supported by regulatory initiatives from agencies like the FDA and guidelines from the International Council for Harmonisation (ICH). Despite the promise of CM, challenges remain, including high initial investment costs, regulatory uncertainties, and a workforce skills gap. The future of CM looks bright, with potential expansions into biopharmaceuticals and personalized medicine, as well as growing global adoption. Ultimately, Continuous Manufacturing represents a paradigm shift in drug production, enhancing efficiency, quality, and affordability, and positioning itself at the centre of the evolving pharmaceutical landscape.

Continuous Manufacturing

Continuous Manufacturing (CM) has emerged as a transformative approach within the pharmaceutical industry, characterized by the constant and uninterrupted flow of production processes. Unlike the traditional batch manufacturing model, which is segmented into discrete steps with frequent downtime between stages, CM operates as a seamless, end-to-end process where raw materials are continuously fed into the system and the final product is consistently produced.

This shift from batch to continuous manufacturing is significant because of the inherent complexity and precision required in pharmaceutical production. Traditional batch methods can be time-consuming, often requiring extensive setup and validation between batches. Furthermore, these processes are susceptible to variability between batches, increasing the risk of product inconsistencies, contamination, or waste. CM, on the other hand, mitigates these issues by maintaining a steady production flow, which allows for more precise control and real-time monitoring.

The pharmaceutical industry is under constant pressure to innovate in order to meet increasing regulatory, economic, and societal demands. As a result, continuous manufacturing has been recognized as a key innovation capable of addressing many of these challenges. For instance, the growing complexity of modern drug products,

particularly in the fields of biologics and personalized medicine, necessitates a more flexible and efficient manufacturing approach. CM's ability to deliver high-quality, consistent products more efficiently positions it as a crucial tool for the future of pharmaceutical production.

Batch Manufacturing vs. Continuous Manufacturing

The traditional batch manufacturing process has served the pharmaceutical industry for decades, and while it has been effective, it is not without limitations. In batch manufacturing, raw materials are processed in a series of steps, often with time-consuming breaks for quality control and equipment cleaning. Each stage of production is completed in isolation before the next stage begins, which can lead to inefficiencies, increased operational costs, and potential quality control issues.

Batch manufacturing also tends to require larger production facilities and more labor-intensive processes. This results in higher costs, both in terms of capital investment and operational expenses. Furthermore, the inherent stop-and-start nature of batch production can create bottlenecks, making it difficult to scale up production quickly in response to fluctuating demand. This is particularly problematic in situations where rapid drug availability is critical, such as during global health crises like the COVID-19 pandemic.

Continuous manufacturing, by contrast, offers a streamlined solution to these challenges. In CM, the entire production process is interconnected, with raw materials flowing continuously through the system. This allows for real-time monitoring of critical parameters, such as temperature, pressure, and concentration, which can be adjusted dynamically to ensure optimal production conditions. The result is a more efficient, cost-effective, and flexible manufacturing system that is better suited to the demands of modern pharmaceutical production.

Benefits of Continuous Manufacturing

The benefits of continuous manufacturing in the pharmaceutical industry are numerous, including improved efficiency, enhanced product quality, and greater agility in responding to market demands. CM offers the following advantages over traditional batch processes:

Improved Efficiency: Continuous manufacturing reduces production times by eliminating the need for lengthy setup and breakdown periods between batches. This allows for a faster overall production cycle and a quicker time to market for new drugs.

Cost Savings: By reducing downtime, waste, and labor requirements, CM leads to significant cost savings for pharmaceutical manufacturers. Additionally, the ability to monitor and adjust production parameters in real-time minimizes the risk of defective products, further reducing costs associated with recalls and product failures.

Enhanced Product Quality: Continuous monitoring and control of production variables ensure that each unit of the final product meets the same high standards. This consistency is particularly important in pharmaceuticals, where even small deviations in product quality can have serious consequences for patient safety.

Agility and Flexibility: CM's continuous nature allows for more rapid adjustments to production volumes, making it easier for manufacturers to respond to changes in market demand. This flexibility is especially valuable for products with variable or seasonal demand, such as vaccines or personalized medicines.

Sustainability: CM processes are typically more energy-efficient and generate less waste than traditional batch manufacturing. This not only reduces the environmental impact of pharmaceutical production but also contributes to cost savings.

These advantages have led to increasing interest in CM from pharmaceutical companies, regulatory agencies, and industry stakeholders alike.

Key Drivers Behind the Shift to Continuous Manufacturing

The shift toward continuous manufacturing in the pharmaceutical industry is being driven by several key factors, including regulatory support, the adoption of Quality by Design (QbD) principles, the need for increased efficiency, cost reduction, and enhanced supply chain flexibility.

Regulatory Support

Regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have been strong advocates of continuous manufacturing in recent years. Recognizing the potential for CM to improve product quality and streamline production, these agencies have actively encouraged pharmaceutical companies to adopt this innovative approach.

The FDA, in particular, has played a critical role in promoting CM through the publication of guidance documents, the introduction of programs like the Emerging Technology Program (ETP), and the approval of drugs manufactured using continuous processes. The ETP, launched in 2014, aims to support manufacturers in implementing new and innovative manufacturing technologies, including CM. Through this program, the FDA provides companies with early engagement and regulatory advice, helping to reduce the risks and uncertainties associated with adopting CM.

In 2016, the FDA granted its first approval for a drug produced using continuous manufacturing, Johnson & Johnson's HIV treatment, Prezista. This milestone marked a turning point for the industry, demonstrating that CM could meet the stringent regulatory requirements for pharmaceutical production. Since then, several other drugs have been approved for production using CM, further solidifying its place in the industry.

Quality by Design (QbD)

Quality by Design (QbD) is a fundamental concept in pharmaceutical manufacturing that emphasizes the importance of designing processes to ensure product quality from the outset. Rather than relying solely on final product testing to confirm quality, QbD encourages manufacturers to understand and control variability within the production process itself. This approach aligns closely with the principles of continuous manufacturing.

In traditional batch manufacturing, quality is often assessed after the production process has been completed. If defects are detected, entire batches may need to be discarded, leading to significant waste and increased costs. Continuous manufacturing, on the other hand, allows for real-time monitoring of critical quality attributes during production. This enables manufacturers to identify and correct deviations as they occur, reducing the risk of defective products and improving overall process efficiency.

The integration of QbD into continuous manufacturing processes ensures that products are consistently manufactured to the highest quality standards. This is particularly important in the production of complex biologics and personalized medicines, where even minor deviations in product quality can have significant implications for patient safety and efficacy.

Efficiency Gains

The efficiency gains associated with continuous manufacturing are perhaps one of its most compelling advantages. By eliminating the need for batch processing and reducing downtime between production runs, CM allows for faster and more streamlined drug production. This is particularly important in the context of modern pharmaceutical manufacturing, where the demand for new drugs is increasing, and the time to market is critical.

In batch manufacturing, production often involves multiple steps that must be performed sequentially, with quality checks and equipment cleaning required between each stage. This can lead to lengthy production times and increased costs. Continuous manufacturing, by contrast, allows for the integration of these steps into a single, uninterrupted process, significantly reducing production times.

In addition to faster production cycles, CM also offers real-time monitoring and control of critical process parameters, such as temperature, pressure, and concentration. This enables manufacturers to make adjustments on the fly, ensuring that the production process remains within optimal operating conditions. The ability to monitor and control production in real time also reduces the risk of defects and improves overall product quality.

Cost Reduction

Cost reduction is a major driver of the shift toward continuous manufacturing. Pharmaceutical companies are constantly seeking ways to reduce operational costs while maintaining high standards of quality and compliance. CM

offers several avenues for cost savings, including lower labor costs, reduced energy consumption, and minimized waste.

In batch manufacturing, labor costs can be significant, as workers are required to set up, monitor, and break down equipment between production runs. CM reduces the need for manual interventions, as the process operates continuously with minimal downtime. This leads to lower labor costs and increased operational efficiency.

Energy consumption is another area where CM can lead to cost savings. Continuous processes are generally more energy-efficient than batch processes, as they eliminate the need for frequent startups and shutdowns. This not only reduces energy costs but also contributes to the overall sustainability of the manufacturing process.

Waste reduction is another important benefit of continuous manufacturing. In batch processes, defects or inconsistencies can result in the need to discard entire batches of product, leading to significant waste and increased costs. CM's real-time monitoring capabilities allow manufacturers to identify and correct issues as they arise, reducing the likelihood of defects and minimizing waste.

Supply Chain Flexibility

The pharmaceutical supply chain is subject to numerous challenges, including fluctuating demand, regulatory requirements, and the need for rapid response to public health emergencies. Continuous manufacturing offers greater flexibility in managing these challenges by allowing manufacturers to adjust production volumes in real-time.

For example, in the event of a sudden increase in demand for a particular drug, such as during a pandemic or public health crisis, CM enables manufacturers to quickly ramp up production without the need for lengthy setup times. This agility is particularly valuable for vaccines, biologics, and personalized medicines, which often require rapid production and distribution to meet urgent healthcare needs.

Continuous manufacturing also simplifies inventory management, as the steady flow of production reduces the need for large stockpiles of raw materials and finished products. This contributes to a more efficient and responsive supply chain, allowing manufacturers to better manage their resources and reduce costs.

Improved Product Quality

One of the most significant advantages of continuous manufacturing is its ability to consistently produce high-quality products. In traditional batch manufacturing, variability between batches can lead to inconsistencies in product quality, which can result in defective products, recalls, and potential harm to patients. CM, by contrast, allows for continuous monitoring and control of production parameters, ensuring that each unit of the final product meets the same high standards.

The real-time monitoring capabilities of CM also allow for more precise control of critical quality attributes, such as drug potency, purity, and stability. This reduces the risk of defects and ensures that products are manufactured to the highest standards of quality and safety.

In addition to improving product quality, CM also reduces the likelihood of product recalls, which can be costly and damaging to a company's reputation. By ensuring consistent product quality throughout the production process, CM helps pharmaceutical companies avoid the financial and reputational risks associated with defective products.

Technological Innovations Driving CM Adoption

The adoption of continuous manufacturing in the pharmaceutical industry has been facilitated by several key technological innovations, including Process Analytical Technology (PAT), automation and digitalization, modular production systems, and single-use technologies.

Process Analytical Technology (PAT)

Process Analytical Technology (PAT) is a system used to design, analyze, and control pharmaceutical manufacturing processes through real-time measurements of critical quality attributes. In the context of continuous manufacturing, PAT tools play a critical role in ensuring that the production process remains within optimal operating conditions.

PAT tools monitor critical process parameters such as temperature, pressure, and concentration in real time, allowing manufacturers to adjust these parameters as needed to

ensure consistent product quality. This level of real-time control is not possible in traditional batch manufacturing, where quality checks are typically performed at the end of the production process.

The integration of PAT into continuous manufacturing processes enables manufacturers to detect and correct deviations from optimal conditions before they result in defective products. This not only improves product quality but also reduces waste and increases overall production efficiency.

Automation and Digitalization

Automation and digitalization are critical components of continuous manufacturing. Advanced automation systems allow for the seamless integration of various production stages, reducing the need for manual interventions and ensuring consistent operation.

In a continuous manufacturing system, automation reduces the likelihood of human error and ensures that the production process operates smoothly and efficiently. Automated systems can monitor and adjust critical process parameters in real time, ensuring that the production process remains within the desired specifications.

Digitalization also plays a key role in CM by enabling the collection and analysis of vast amounts of data. This data can be used to optimize production processes, identify potential issues before they become problematic, and improve overall production efficiency. By leveraging data analytics and digital platforms, pharmaceutical companies can gain valuable insights into their manufacturing processes and make more informed decisions about how to improve efficiency and product quality.

Modular Production Systems

Modular production systems are another important innovation that supports the adoption of continuous manufacturing in the pharmaceutical industry. In a modular system, each unit operation (such as mixing, granulation, or tablet pressing) is interconnected in a flexible and scalable manner. This allows manufacturers to customize their production lines according to the specific needs of different products.

Modular systems are particularly advantageous for smaller production volumes, such as those required for personalized medicines. They also offer greater scalability, making it easier to expand production capacity as needed. For example, a modular system can be reconfigured or expanded to accommodate new products or changes in production demand without the need for extensive re-engineering.

In addition to providing flexibility, modular production systems also enhance process efficiency and reduce downtime. By enabling the rapid reconfiguration of production lines, modular systems allow manufacturers to quickly adapt to changes in product formulations or market demand.

Single-use Technology

Single-use technologies have gained significant traction in the biopharmaceutical sector, where they play a critical role in enabling continuous biomanufacturing. Single-use bioreactors and other disposable components help reduce the risk of cross-contamination, simplify cleaning procedures, and speed up the production process.

In traditional batch manufacturing, equipment must be thoroughly cleaned and sterilized between production runs to prevent contamination. This can be time-consuming and costly, particularly in the production of biologics, where stringent sterility and cleanliness standards are required. Single-use technologies eliminate the need for these cleaning procedures, allowing for faster and more efficient production.

Single-use technologies are especially valuable in the production of biologics, such as monoclonal antibodies and vaccines, where maintaining sterility is critical. By reducing the risk of contamination and simplifying production processes, single-use technologies help biopharmaceutical companies improve efficiency and reduce costs.

Pharmaceutical Companies Leading the CM Transition

Several major pharmaceutical companies have made significant investments in continuous manufacturing, leading the way in adopting this innovative approach to drug production. These companies have recognized the potential of CM to improve efficiency, reduce costs, and enhance product quality.

Johnson & Johnson

Johnson & Johnson has been a pioneer in the adoption of continuous manufacturing. In 2016, the company received FDA approval for Prezista, an HIV treatment produced using CM. This approval marked a major milestone for the pharmaceutical industry, demonstrating the feasibility and effectiveness of continuous manufacturing in drug production.

Since then, Johnson & Johnson has continued to invest in CM technologies to enhance its manufacturing capabilities. The company has been a strong advocate for the adoption of continuous manufacturing, recognizing its potential to improve efficiency, reduce costs, and enhance product quality.

Pfizer

Pfizer has also embraced continuous manufacturing, particularly for the production of solid oral dosage forms. The company has integrated CM into its operations to improve production efficiency and reduce its environmental footprint.

By adopting continuous manufacturing, Pfizer has been able to streamline its production processes and respond more rapidly to changes in market demand. The company's use of CM has also contributed to a reduction in waste and energy consumption, further enhancing its sustainability efforts.

Novartis

Novartis has been at the forefront of developing and implementing continuous manufacturing technologies. In collaboration with the Massachusetts Institute of Technology (MIT), the company has been working to create smaller, more agile production facilities that can adapt quickly to changes in product demand.

This collaboration has positioned Novartis as a leader in the transition to CM, and the company continues to invest in research and development to further advance its manufacturing capabilities. Novartis's focus on continuous manufacturing is driven by its commitment to improving efficiency, reducing costs, and delivering high-quality products to patients more quickly.

Vertex Pharmaceuticals

Vertex Pharmaceuticals became one of the first companies to receive FDA approval for a continuously manufactured drug, Orkambi, which is used to treat cystic fibrosis. This approval was a significant achievement for the company and highlighted the potential of continuous manufacturing to produce complex, high-quality medications more efficiently than traditional batch processes.

Since then, Vertex has continued to invest in continuous manufacturing technologies to enhance its production capabilities and improve the efficiency of its operations. The company's success with Orkambi has demonstrated the feasibility of CM for producing complex therapies and has paved the way for further adoption of continuous manufacturing in the industry.

Regulatory and Industry Collaboration

The adoption of continuous manufacturing in the pharmaceutical industry has been facilitated by close collaboration between regulatory agencies, industry stakeholders, and academic institutions. This collaboration has been instrumental in overcoming some of the challenges associated with implementing CM and has helped to accelerate its adoption.

FDA Initiatives

The FDA has been a key driver of continuous manufacturing adoption through its Emerging Technology Program (ETP). The ETP was established to support pharmaceutical companies in implementing innovative manufacturing technologies, including CM. Through this program, the FDA provides companies with early engagement and regulatory advice, helping to reduce the risks and uncertainties associated with adopting continuous manufacturing.

The FDA's approval of the first continuously manufactured drug, Johnson & Johnson's Prezista, was a significant milestone for the industry. Since then, the FDA has continued to provide guidance and support to manufacturers looking to adopt CM, further promoting its use in the pharmaceutical industry.

ICH Guidelines

The International Council for Harmonisation (ICH) has also played a key role in supporting the adoption of continuous manufacturing. The ICH has issued several guidelines aimed at facilitating the implementation of CM, including ICH Q13, which

provides a framework for the continuous manufacturing of drug substances and products.

These guidelines offer pharmaceutical companies a clear regulatory pathway for adopting continuous manufacturing while ensuring that product quality and safety are maintained. The ICH's efforts have been instrumental in promoting the global adoption of CM and ensuring that regulatory requirements are harmonized across different regions.

Collaborative Partnerships

Collaborative partnerships between academic institutions, regulatory bodies, and pharmaceutical companies have been critical to the development and implementation of continuous manufacturing technologies. For example, the collaboration between Novartis and MIT has played a key role in advancing the understanding and application of CM in the pharmaceutical industry.

These partnerships have helped to accelerate research and development efforts, leading to the creation of new technologies and processes that support continuous manufacturing. By fostering collaboration between industry stakeholders, these partnerships have also helped to overcome some of the challenges associated with implementing CM, such as the need for specialized expertise and the development of new regulatory frameworks.

Challenges in Adopting Continuous Manufacturing

Despite the many advantages of continuous manufacturing, there are several challenges that have hindered its widespread adoption in the pharmaceutical industry. These challenges include high initial investment costs, regulatory uncertainty, technological complexity, and a workforce skills gap.

High Initial Investment

One of the primary barriers to adopting continuous manufacturing is the high initial investment required to set up a continuous manufacturing line. CM involves significant capital expenditure on new equipment, infrastructure, and technology, which can be a major obstacle for smaller pharmaceutical companies with limited resources.

However, as CM technologies become more widespread and the costs associated with their implementation decrease, it is expected that these barriers will diminish. In the meantime, larger pharmaceutical companies with the resources to invest in CM are leading the way in adopting this innovative approach.

Regulatory Uncertainty

While regulatory agencies have been supportive of continuous manufacturing, the guidelines surrounding its implementation are still evolving. This regulatory uncertainty can make it difficult for companies to ensure compliance and validate their CM processes. As more drugs are approved for production using continuous manufacturing, it is expected that the regulatory landscape will become clearer, reducing the uncertainties associated with CM.

Technological Complexity

Continuous manufacturing requires advanced technologies such as Process Analytical Technology (PAT), automation systems, and real-time monitoring tools. Integrating these technologies into existing production lines can be challenging, particularly for companies that lack the necessary technical expertise or experience.

In addition to the technical challenges associated with implementing CM, companies must also invest in the training and development of their workforce to ensure that employees have the skills needed to operate and maintain these advanced systems.

Workforce Skills Gap

The shift to continuous manufacturing demands a workforce with new skills in areas such as automation, process control, data analytics, and real-time monitoring. Ensuring that employees are adequately trained to operate and maintain CM systems is a significant challenge for many pharmaceutical manufacturers.

Companies must invest in training programs and workforce development initiatives to bridge this skills gap and ensure that their employees are equipped to handle the demands of continuous manufacturing.

The Future of Continuous Manufacturing in Pharmaceuticals

The future of continuous manufacturing in the pharmaceutical industry looks

promising. As regulatory support continues to grow and technological advancements drive down costs, it is expected that CM will become more widely adopted across the industry.

Expansion into Biopharmaceuticals

One of the most exciting areas of development in continuous manufacturing is its application to biopharmaceuticals. Continuous biomanufacturing (CBM) is gaining momentum, particularly for the production of complex biologics such as monoclonal antibodies and vaccines.

Biopharmaceuticals are typically more challenging to produce than small-molecule drugs, due to their complexity and the need for stringent quality control. However, continuous biomanufacturing offers significant advantages in terms of efficiency, scalability, and product quality. By enabling real-time monitoring and control of critical process parameters, CBM allows manufacturers to produce biologics more efficiently and with greater consistency.

The development of single-use technologies has also played a key role in the growth of continuous biomanufacturing. Single-use bioreactors and other disposable components reduce the risk of contamination, simplify cleaning procedures, and speed up the production process, making CBM an attractive option for biopharmaceutical companies.

Personalized Medicine

The flexibility of continuous manufacturing makes it an ideal solution for the production of personalized therapies, such as cell and gene therapies. These therapies often require smaller, more agile production systems that can be easily adapted to individual patient needs. Continuous manufacturing is well-suited to meet these requirements, making it a valuable tool in the era of personalized medicine.

As the demand for personalized therapies continues to grow, it is expected that continuous manufacturing will play an increasingly important role in the production of these treatments. CM's ability to produce small, customized batches of drugs more efficiently and with greater consistency makes it an ideal solution for personalized medicine.

Global Adoption

As regulatory frameworks mature and the costs of continuous manufacturing technologies decrease, it is expected that CM will become more widely adopted globally. Both developed and emerging markets are likely to embrace continuous manufacturing, further transforming the pharmaceutical manufacturing landscape.

In developed markets, regulatory support and the need for greater efficiency and product quality will drive the adoption of CM. In emerging markets, the ability to produce drugs more cost-effectively and with greater flexibility will make CM an attractive option for pharmaceutical manufacturers.

Conclusion

The pharmaceutical industry's shift toward continuous manufacturing represents a significant paradigm shift in how drugs are produced. With its potential to enhance efficiency, product quality, and cost-effectiveness, CM is poised to become a cornerstone of the future pharmaceutical landscape.

Regulatory support, technological advancements, and industry collaboration have all contributed to the growing adoption of continuous manufacturing. While challenges such as high initial costs and regulatory uncertainties remain, the benefits of continuous manufacturing far outweigh the obstacles.

As the industry continues to innovate and adapt, continuous manufacturing will play an increasingly vital role in ensuring that patients receive safe, effective, and affordable medications in a timely manner. The future of pharmaceutical manufacturing is undoubtedly continuous, and the industry is well on its way to embracing this transformative approach.

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Industrial Pharmaceutical Microbiology: Quality Control

Edited by Edward Tidswell and Radhakrishna Tirumalai

Industrial Pharmaceutical Microbiology: Quality Control provides an in-depth comprehensive survey of QC pharma methods in the microbiology laboratory, to enable a better understanding of these methods, and to ensure better developed, more compliant, expedited procedures.

The reference text brings together the hitherto unavailable background, fundamental science, principles, development, intended purpose, and specific answers to questions of execution and qualification of compendial and related microbiological test methods. Key topics include the types of microbiological tests, reference strains and culture collections, and equivalence of reference strain.

Test methods and subject matter include bioburden, microbial enumeration, specified and objectionable microorganisms, antimicrobial effectiveness testing, endotoxins and sterility tests, microbial identification, biological indicators, water activity, disinfectant efficacy, and water. It also covers a critical, stimulating look into the topic of Environmental Monitoring.

In summary, ***Industrial Pharmaceutical Microbiology: Quality Control*** with its 20 chapters, 19 international authors and over 500 pages, enables the practitioner to have a complete understanding of these microbiological methods, and to ensure better developed, compliant, appropriate procedures and accurate meaningful data.

https://euromedcommunications.com/collections/pharmaceutical-sciences-manuals/products/industrial-pharmaceutical-microbiology-quality-control

Process for Reducing Bioburden in Water Systems

by Fritz Röder

Water is one of the most important starting materials for the production of pharmaceuticals and has a decisive influence on product quality. It is therefore subject to defined quality attributes. This includes microbiological quality, which can be particularly affected by the formation of biofilms. Regular disinfection of the water generator and the storage and distribution system is the only way to prevent biofilm formation. It also serves as a quality assurance measure after maintenance. A distinction is made between hot sanitisation, where the system is rinsed with hot water, cold sanitisation using ozone and chemical sanitisation using, for example, H_2O_2 as a disinfectant. In addition to sanitisation, there is also the option of sterilisation with pure steam or chemical disinfection. However, both of these methods are less important than sanitisation.

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Introduction

Despite the high quality demands placed on the execution and design of water production plants as well as storage and distribution systems, it cannot be excluded that bacteria enter such a system. For this reason, samples are regularly taken and tested for microbial counts.

Measures to reduce the microbial count should generally be taken preventively at fixed intervals and described accordingly. It is not permissible to start appropriate measures "only after an infestation has occurred." Inspectors generally expect operators to implement a preventive program.

A distinction is made between the *terms* "sanitisation," "sterilisation" and "disinfection."

Sanitisation

Microbes are present in every source of raw water. The various process stages (softening plant, reverse osmosis and EDI) as well as the treated water distribution system and the sanitisation concept must be adapted to the site-specific conditions. Here it is important that the sanitisation concept fits the plant and is therefore effective. Not every sanitisation process can be used universally. For example, reverse osmosis membranes are neither chlorine nor ozone resistant.

In terms of *process technology,* a distinction is made between the sanitisation concept for the treatment plant and that for the storage and distribution system.

The following general *methods* are available for sanitisation:

- Heat
- Ozone
- Other chemicals, such as
  - Hydrogen peroxide
  - Peracetic acid
  - Chlorine compounds
  - Caustic soda
  - Citric acid

At every point in the plant, the required temperature or chemical concentration must be reached as described in the sanitisation concept. Nevertheless, a plant is never "completely free of microbes" after sanitisation. In contrast to sterilisation, sanitisation cannot be defined as an precise minimum depletion of the microbial count. During sanitisation, the system is not available, i.e. not operational (exception: hot storage).

Regular, preventive sanitisation can prevent the formation of biofilm and thus also the exceeding of bioburden limits.

The *frequency* of sanitisation measures cannot be determined across the board. Sanitisation must be done at a minimum for instances after the water system

Sanitisation

Sanitisation includes measures that go beyond regular cleaning in order to achieve an extensive reduction of microorganisms. However, sanitisation does not provide a claim to extensive or complete sterility, as would be the case with disinfection or sterilisation. Water treatment plants are sanitised, not disinfected. A complete inactivation of microorganisms with common cleaning methods cannot be guaranteed.

Sterilisation

Sterilisation means making an object or system completely microbe-free. The theoretical depletion of microorganisms is set to a factor of 10^{-6}.

Disinfection

The term disinfection describes the reduction of germ counts by various measures by five powers of ten, i.e. by 99.999%. According to the German Pharmacopoeia, after disinfection "dead or living organic material should no longer be able to infect." Theoretically, ten out of one million germs may still survive after disinfection.

has been "opened," as this removes the "controlled state" of the water system. Such an "opening" would include, for example, maintenance of the water system.

The *frequency* with which water systems are sanitised varies greatly in practice and ranges from daily to semi-annually, and in isolated cases possibly even annually. In addition, hot storage of water, for example, is referred to as "permanent sanitisation" or "self-sanitisation." Such systems are very robust and not very error-prone, but they are very energy-intensive. Furthermore, the operating mode and the feed water quality have an influence on the sanitisation frequency. If the water in the system is frequently consumed or disposed and replenished, the frequencies can possibly be extended.

Hot sanitisation

Hot sanitisation is carried out by heating the water to a temperature of 65–80°C at the coldest point in the system. For this purpose, the ultrapure water circulating in the distribution system is heated to the specified sanitising temperature with a heat exchanger and kept at the sanitising temperature for the specified holding time. The duration of the sanitisation depends essentially on the coldest point of the water system. This point must be determined beforehand as part of the qualification process; it is often found in the return or directly upstream of the heat exchanger. The holding time is determined by the water system and its condition. Holding times of 1 to 4 hours have been proven effective in practice. Including heating and cooling, a total sanitisation time of 2–12 hours can therefore normally be expected. After sanitisation, the heated water is cooled down again. This is done either with a heat exchanger (heating/cooling combination) or by discharging the hot water and feeding fresh, cold ultrapure water.

Most bacteria found in ultrapure water are reliably killed at a temperature of 70°C. Sanitising, if performed regularly, is therefore an effective preventive measure to avoid accumulation of microbes in the system and the formation of biofilms. It is pointed out according to USP <1231>, Section 8.1.5 that even thermophilic germs cannot survive long-term in ultrapure water systems because the supply of nutrients is insufficient. To date, no species is known which survives permanently in hot ultrapure water systems.

For the piping system it must be noted that the expansion occurring during heating can be compensated (natural compensation of thermal expansion by symmetrical bends (expansion loop) and simple angular bends (expansion offset)). All components installed in the system must be resistant to the sanitising temperature.

Cold sanitisation

Cold sanitisation is usually understood to mean sanitisation with ozone. In pharmaceutical water systems, ozone treatment is only possible for the ultrapure water storage and distribution system. The treatment unit cannot be exposed to ozone as this would damage the RO membranes. The treatment unit is therefore usually still heated periodically.

Ozone has the following advantages over thermal methods:

- Ozone decomposes without leaving residue and can be produced cost-effectively on site. The CO2 footprint of ozonized systems is significantly lower than that of hot sanitised systems or hot storage.
- By-products and residues are not formed during sanitisation with ozone.
- The required quantities can be easily adjusted.
- Ozone is metastable in water and decays to oxygen with a half-life of 20 to 60 minutes.

In ozonized systems, the storage tank is usually maintained continuously under an ozone blanket. The ozone in the ultrapure water is destroyed with a UV lamp (254nm) in the feed to the loop. The UV lamp must be designed to ensure this requirement. The natural ageing process of the lamps should also be taken into account. An ozone meter downstream of the UV lamp monitors down to the detection limit (approx. 5 ppb) for the presence of ozone in the system to monitor its effectiveness.

Sanitisation of the entire ring system can be accomplished by turning off the UV lamp, allowing the ozonated water to flow through the entire ring. In this case, the ozone meter is used to monitor that the required concentration is achieved in sanitisation mode.

In practice, ultrapure water storage and distribution systems are often sanitised regularly overnight or at weekends with a concentration of 20ppb to 100ppb. However, the exact procedure regarding sanitisation interval, ozone concentration and sanitisation duration must be specified by each operating company for the respective system. The half-life of the ozone in the system must be taken into account. This is very much related to the TOC and the bioburdens in the system: with a high TOC content or high bioburdens, ozone is degraded more quickly. Modern systems have a relatively low TOC content and low bioburdens. These systems can be operated permanently with approx. 30ppb ozone without any problems.

It should be noted, however, that the ozone concentration should not be selected too high, since with increasing concentration ozone also increasingly attacks the elastomers of the seals (for example EPDM) and measurement devices in the system. With ozone concentrations of 20 to 50ppb, good sanitisation results can be achieved with a correspondingly long sanitisation time.

When sanitising with ozone, it is important to ensure that the ozone concentration in the entire system does not fall below the target concentration. This can be ensured by monitoring the return flow of the system, for example with an additional ozone sensor. Due to the physical-chemical relationships, however, it is expected that the ozone will be distributed relatively quickly in the system so that a uniform concentration results.

In addition to the advantages offered by an ozonated system, however, there are some disadvantages: it is more difficult to sanitise the sampling points with ozone than with hot sanitized systems. Two basic problems arise here:

1. **Ozone distribution:** It is more difficult to achieve a sufficient level of ozone in the outlet valves than it is with heat. With heat, the pipeline walls are also heated, and these conduct the heat to remote locations in the pipeline. This is not the case with ozone. Therefore, even closer attention must be paid here to ensuring that the system is free of dead spaces.
2. **Flushing of use points:** It is easy to open the taps in a heated system for a period of time and discharge hot water. Apart from the risk of scalding, there is nothing else to watch out for. When water is drawn from an ozonated system however, ozone will off-gas in the room to a small degree and may become concentrated. This poses a potential health risk. A safety analysis is necessary here. Overall, however, at a concentration of approx. 50ppb in the loop with a rinsing duration of 10 seconds, the workplace limit value should be reliably undercut. Nevertheless, a case-by-case consideration is always necessary.

Sterilisation process

The standard European Pharmacopoeia procedure for sterilisation uses pressurised steam (pure steam) for 15min at 121°C, or for 3min at 134°C. In terms of water systems, this means pure steam is fed into the storage and distribution system, which then flows through the piping system and the tanks.

This process is rarely found in practice today because, although it is very effective, it entails various additional requirements (e.g. safety measures with regard to pressure and temperature, material resistance, expansion effects). Moreover, the process is not preferred from a sustainability point of view. In addition, it has also been shown in practice that completely adequate results can already be achieved with temperatures around 70°C (i.e. sanitisation, not sterilisation).

If one nevertheless decides to use a sterilisable system, the following must be observed:

- To discharge the condensate produced, condensate drains must be provided at all low points in the system and, in the case of longer pipelines, at specific intervals.
- At a minimum, temperature sensors must be installed at these low points (or at the potentially coldest points) to monitor the sterilisation temperature and document that no condensate was present at the low points during sterilisation, thus preventing sterilisation at that point.
- The storage containers of systems that are to be sterilised must have a pressure resistance that corresponds to the pure steam pressure of the sterilisation temperature.
- For the piping system, it must be ensured that the expansion occurring during heating can be compensated (natural compensation of thermal expansion by expansion loops and offsets) and that none of the components installed in the system are damaged by the sterilisation temperature.

For more information on the generation and distribution of pure steam.

As mentioned above, water storage and distribution systems are rarely sterilised with pure steam in practice. For generation systems, sterilisation with steam is basically not possible due to the lack of tolerance to these conditions. In addition to the design effort mentioned above, the issue of energy and sustainability also plays an increasingly important role. It can therefore be assumed that the sterilisation of water systems with steam will be used less.

Disinfection

Chemical disinfection of water systems is only recommended if (preventive) microbe reduction cannot be achieved by other methods (for example ozone, hot water, ultrapure steam). A second case where disinfectants are very helpful is the control of an established biofilm.

Hydrogen peroxide or peracetic acid, for example, are used as disinfectants, as these offer a broad spectrum of activity against bacteria. Ready-configured products from various producers are available on the market for this purpose. When disinfecting, it must be taken into account that rinsing out the disinfectants in storage and distribution systems can be very time-consuming and must be reflected in planning and execution (depending on the performance of the water treatment system). The proof of the presence and absence of the disinfectant is done manually with test sticks at all relevant treatment or withdrawal points. Accordingly, significantly longer downtimes must be expected here than with hot sanitisation or ozonisation.

Disinfection is carried out, for example, in water treatment plants that are unsuitable for hot sanitisation due to their design and membranes. The use of ozone is generally ruled out for purified water generation plants, as the reverse osmosis membranes cannot tolerate ozone and are damaged by it. One German manufacturer known to the author uses ozone in the softening and ultrafiltration stages (ambient WFI).

As with hot sanitisation or ozonisation, sufficiently high concentrations and treatment times are important for chemical disinfection. When combating established biofilms, caustic soda has proven to be a helpful agent, best followed by further disinfection steps with other agents. Typically, caustic soda is dosed up to pH13 for this purpose (provided the system tolerates it), the required treatment time is approx. 3 hours.

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Risk Review and Monitoring

by James Vesper and Amanda McFarland

Monitoring and review have an important function in a risk management program by helping to ensure that the quality and effectiveness of risk assessments performed – and the controls that are implemented as a result – meet high standards. This is a sample chapter from the new book *Quality Risk Management* and is reprinted here with the kind permission of the authors.

James Vesper designs and develops instructional courses and workshops for the pharmaceutical and biopharma industries at ValSource, Inc. He has had more than 40 years' experience in the pharmaceutical industry, including eleven years at Eli Lilly and Company. His areas of interest include GMPs, contamination control, Quality Risk Management, root cause investigations, knowledge management, and learning & performance solutions. Dr Vesper has written six books. He has taught at the PDA Training and Research Institute, has been co-lead for PDA task force on knowledge management and spoken at PDA Annual Meetings, PDA/FDA Joint Conference, IMRP, and the Association for GXP Excellence and taught in-house courses for a wide range of international clients including WHO and PIC/S.

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Introduction

Risk review and monitoring is an important but often neglected phase in the quality risk management process. Once the risk assessment is completed, it often sits on the shelf or on a server and not looked at again. However, review and monitoring is used to capture new knowledge and experience. Knowledge should be kept up-to-date by considering any changes to the process or product that was the subject of the risk assessment. The purpose of this chapter is to present the rationale for risk review and monitoring and provide specific considerations on how it can be accomplished.

Advantages of Risk Review

Reviewing the output of a risk management exercise and monitoring what was assessed takes planning, time, and resources. However, there are many benefits and these include:

- Ensuring that risk controls are achieving their intended purpose.
- Verifying that assumptions used in the analysis are correct.
- Determining if any unrecognized hazards are present.
- Helping detect changes that could affect the assessments.
- Reducing uncertainty due to incomplete or inadequate knowledge.
- Contributing information to product quality reviews and annual regulatory reports.
- Driving process and product improvements.

It is important to note that, not all risk assessments are subject to review or monitoring.

If a risk assessment was performed to make a specific decision such as, should a product be recalled or when should an internal site be audited, the risk assessment is not "living"; once the decision is made the assessment becomes part of the history of that decision. On the other hand, risk assessments that have been performed to inform an environmental monitoring plan or a process would be considered "living" and need to be monitored and periodically reviewed.

Review compared to monitoring

Risk review and risk monitoring look at the completed risk management activity from two different points of view: temporal review and event driven review. Temporal review examines, at defined timepoints,

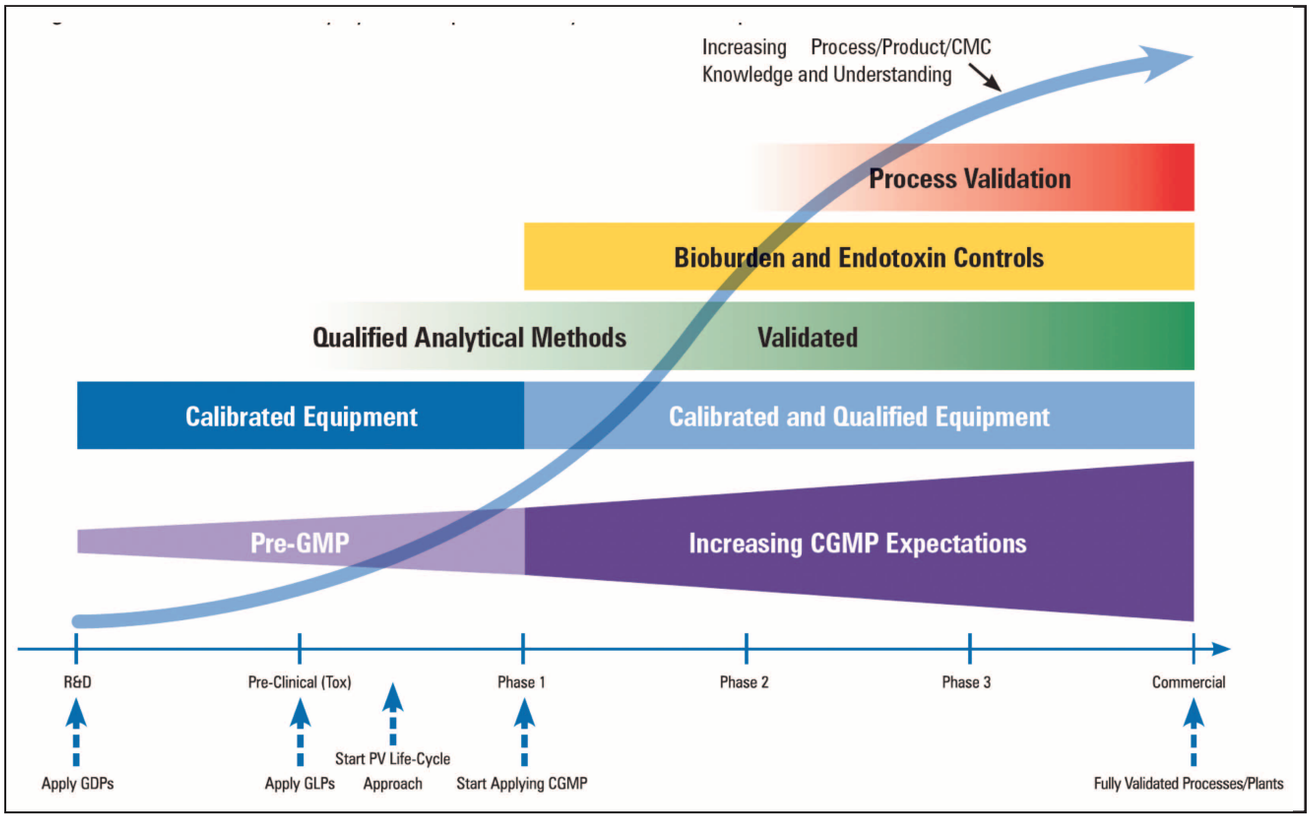


Figure 1. Increasing knowledge during a product's lifecycle[1]. Used with permission from PDA.

the completed document in light of what has occurred since the initial development and subsequent reviews of the risk report; it is a look back in time. For example, is there more data available to support better likelihood estimates? Have any new failure modes been identified? Are the controls still operating as planned?

Risk monitoring, on the other hand, considers events that could trigger a change in the assessment. A change or an unwanted event should prompt a look into the assessment. Examples would include a change in vendors, deviations, or other quality events that might have an impact on the assessment. These could introduce new hazards or change the likelihood estimates that were initially made.

New information to reduce uncertainty and risk

One of the benefits of monitoring and review is gathering information that reduces uncertainty, and with that, reduces risk. Early on in a product's lifecycle, information may not be available or specification ranges could be quite wide; there is a high degree of uncertainty.

As experience is acquired through more test runs, production at scale, and the like, information is generated and uncertainty is reduced. As uncertainty decreases, so does risk because now you know – you have additional knowledge.

In an effective quality system, the knowledge and understanding that is generated through reviewing and monitoring feeds into quality system elements such as qualification, validation, and contamination control as shown in **Figure 1**. The knowledge gained provides confidence that controls are aligned with the hazards and work as intended. Or, the new knowledge may show that improvements need to be made. At the same time, new hazards may appear as incidents, deviations, or consumer complaints that require new controls.

Monitoring and review contribute to achieving the goals stated in the ICH Q10 Pharmaceutical Quality System: "Quality risk management can be useful for identifying and prioritizing areas for continual improvement"[2].

Categories of information to monitor

A now-withdrawn risk management standard from Canada listed six elements that should be monitored[3]:

- The environment where the activity takes place.
- Those things that are exposed to hazards.
- The nature of the hazard itself.
- Acceptability of the risks to the stakeholders.
- Who the stakeholders are.
- Technology that is new, different, or that has changed since the analysis.

Each of these are discussed in more detail below. The term "environment" can include not just the physical environment – the facility, the environmental conditions (including weather) – but also the regulatory environment. When regulations are modified, new guidance documents issued, or expectations changed, such actions may prompt a review of the assessment conducted.

People, items, products, organizational structures and the like that are exposed to a hazardous agent may change, for example, the type of shipping container used for a temperature-controlled item. This could cause potentially more risk, or it could lower the risk that was identified in the risk analysis. The hazard itself could change. Different microbes or levels of bioburden may appear because of a change in vendors.

Changes in climate could have a potential impact on the shipping of temperature-controlled products.

Sometimes, stakeholders become more resistant to certain risks – their risk appetite or risk thresholds may change. They refuse to accept risks at levels that were previously tolerable. This might result from new information about threshold levels that could cause unwanted events or because there is a new analytical method that detects a contaminant at lower levels. Or, there may have been a significant regulatory action against the firm and the organization becomes much more conservative in how it makes compliance-related decisions.

Stakeholders themselves can change. Marketing a product to a new country or region may expose the manufacturing firm to regulatory inspections from different agencies that have different requirements or expectations. People in different markets who use a given product may have differing expectations of that product. For example, they may have less tolerance for subtle cosmetic defects that people in other markets ignore.

The technology in use may change completely or be replaced. For example, inline testing may replace traditional off-line QC laboratory testing. Or, equipment may be modified in some way. The pharmaceutical industry has an advantage over other industries with regard to monitoring. Many of the items described already will be included or monitored by quality system elements such as change control/change management, environmental monitoring, deviation reports and investigations, customer complaints, internal auditing, and product quality reviews.

While conceptually this should make the process easier, it requires thoughtful integration between the quality system, the QRM program, and those responsible for monitoring and review.

Risk Review Plans

The supplemental training materials[4] on risk monitoring and review developed by the ICH Q9(R1) working group discuss having risk review plans that have a two-stage process. For "living" risk assessments, the first stage would include considering the output of the assessment, specifically:

- Defining what should be examined in the review. This might include severity (impact), likelihood, or detectability ratings or the additional controls for some or all of the hazards that were identified.
- Revisiting the assumptions that were made when making decisions to determine their current validity.
- Determining if new information reduces uncertainty that may have been present in the initial and subsequent assessments.

In the second stage the Q9(R1) supplemental training materials suggest looking for new knowledge coming from the quality system that could result in an updated and revised understanding of the risks.

Review Frequency

While monitoring is conducted in an on-going, real-time manner, there is no standard

recommendation for when the outputs of the risk management process should be reviewed. Q9(R1) states that the frequency is based on the level of risk. This would include how robust the risk monitoring activities are. If there is an active monitoring program that has its effectiveness demonstrated, risk reviews or their frequency could be reduced.

Factors to consider when determining a review frequency include how dynamic the knowledge is related to the assessment. In early development of a new product, process knowledge may be increasing daily; a review might be beneficial every six months. For a product or process that has a long, stable history, perhaps every two or three years is adequate. (Note though that monitoring outside events [e.g., changes or deviations] could trigger opening up the documents.) One option for setting the review frequency would be asking the subject matter experts on the risk team to recommend the next review as they should already be familiar with how dynamic the knowledge is.

Risk Register Reviews

Review of the significant risks recorded on a firm's risk register often happens during management meetings or by the firm's board of directors. Being aware of risks that remain or the progress in implementing changes or new controls is something that these leaders need (and usually want) to be involved with.

Often these reviews are documented in the meeting minutes. Fulton, Mains, and Waldron[5] identified seven questions that management should ask when reviewing a risk register:

1. Are mitigations on track to be complete per the approved plan? If not, what actions need to be taken to either achieve the desired timeline or accept a new timeline?
2. Is the scope or intent of the mitigation still meaningful or relevant?
3. Are there other options or improvements that will achieve the same outcome?
4. Are there any unforeseen complications that have been identified during the execution of the changes to implement the mitigation plans?
5. Did executed actions mitigate risk effectively as planned? If not, what needs to be done to improve the mitigation plans to meet expectations?
6. Are there any changes to regulations or the organization's risk tolerance that impact prior decisions or timelines?
7. What observations have been made (internally or externally) that impact prior decisions or timelines?

Conclusion

Conducting risk assessments and implementing the controls used to mitigate risks takes time, resources, and money. Stakeholders depend on the validity of the risk assessment and the successful operation of the controls. Monitoring and review have an important function in a risk management program by helping to ensure that the quality and effectiveness of risk assessments performed – and the controls that are implemented as a result – meet high standards.

References

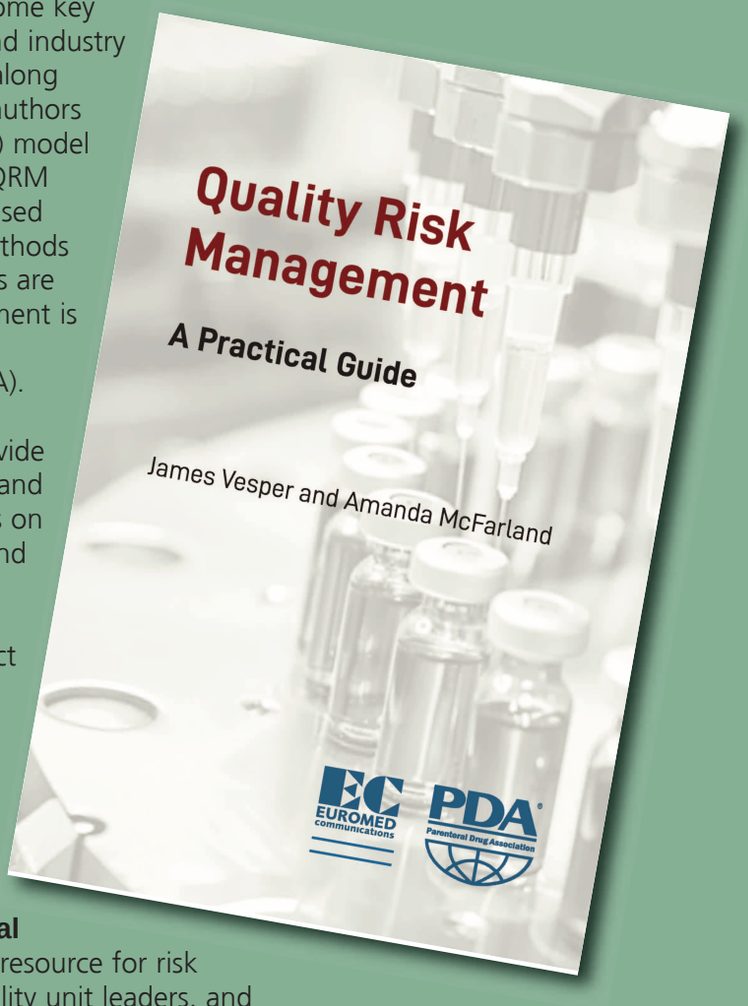
1. PDA Technical Report Number 56. Application of Phase Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance. 2016. Bethesda, MD: PDA.
2. International Council on Harmonization. ICH Q10 *Pharmaceutical Quality System*. 2008. https://www.ich. org/page/quality-guidelines (accessed 22 Nov 2024).
3. Canadian Standards Association. CAN/CSA-Q850-97, Risk management: guideline for decision-makers. 2002. Ontario, Canada.
4. International Council on Harmonization. ICH Q10 *Pharmaceutical Quality System.* 2008. https://database. ich.org/sites/default/files/Q10%20Guideline.pdf (accessed 14 Sep 2024).
5. Fulton B, Mains P, and Waldron K. "Best Practices For Use Of Risk Registers In Biopharmaceutical Manufacturing Operations." *Pharmaceutical Online.* October 2023. https://www.pharmaceuticalonline.com/doc/best-practices-for-useof-risk-registers-in-bio-pharmaceutical-manufacturing-operations-0001 (accessed 21 Nov 2024).

Risk Management – A Practical Guide

By James Vesper and Amanda McFarland

Since the publication of the first Quality Risk Management (ICH Q9) guideline in 2005 and *Risk Assessment and Risk Management in the Pharmaceutical Industry* by James Vesper in 2006, the pharmaceutical industry has made considerable strides in its understanding and application of QRM and risk-based decision making. This evolution is captured in a revised and expanded volume, **Quality Risk Management: A Practical Guide.**

Beginning with a historical context of some key events that have shaped how society and industry think about risks and controlling them along with defining concepts and terms, the authors provide an overview of the QRM Q9(R1) model and do a deeper dive into each of the QRM phases. An emphasis is made on risk-based thinking and bias reduction. Various methods and tools used in doing risk assessments are described, illustrating that risk management is more than just using a singular tool like Failure Mode and Effects Analysis (FMEA).



In twenty-two chapters the authors provide all the information you need to understand the concept of QRM, including chapters on facilitating risk management activities and the connection between risk management and knowledge management. QRM is an essential aspect of the pharmaceutical industry, and this volume is based on the authors' experience as facilitators, risk-tool developers, and instructors to pharma and biopharma risk teams around the world.

Quality Risk Management: A Practical Guide will prove an important and key resource for risk owners, risk assessment facilitators, quality unit leaders, and those who make risk-based decisions.

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bottled brown

Insights into invention

Dr Malcolm E. Brown has degrees in natural and social science research and elected a Fellow of the Royal Pharmaceutical Society (FRPharmS) for distinction in the profession of pharmacy. He has worked in senior positions as a production manager (big Pharma) and in the British NHS including at director level — and as a community pharmacist. He has tutored many future pharmacists and trained the "entire" sales force of a major international company on selling medicines to the NHS. He was the keynote speaker at an international multidisciplinary conference at the Hague. Dr Brown is an award-winning writer with over 160 publications.

These are neither authoritative nor comprehensive. However, some perspectives below just may make all the difference.

The Nobel Laureate in medicine or physiology, Szent-Györgyi (1937) said "discovery consists of seeing what everybody has seen and thinking what nobody has thought". To Szent-Györgyi, knowledge crammed from books had a "half-life" of a few weeks; we should use our heads for something better. But what?

Tool kit

Our go-to tool is the wallop of the scientific method. Something new in the world presents opportunities. For example, COVID-19 offered a new area ripe for tackling by existing expertise. The scientists Sahin and Türeci did so. They developed mRNA technology and fertile fields for development such as cancer treatments beckon.

Marketers may signpost high-return directions. One is menopause mitigation. That is connected with profit — and controversies. Another is increasing myopia worldwide. Low-dose atropine may slow progression. Improving medicine stability is a routine endeavour such as for vaccines. Distribution causes problems within hot climates. One approach is to avoid vaccines that contain large molecules, substituting smaller, more thermostable molecules such as remdesivir. Snake-bite antisera also need refrigeration and the smaller, less thermolabile molecule varespladib, a phospholipase A2S inhibitor, may be effective against lethal bites from vipers.

I now rummage in our toolkit to discover tools that are chosen less frequently.

Borrow from finance. Adapt their "barbell strategy": invest at opposite ends of the spectrum. Devote some time to an area vastly different from your original discipline's comfort zone. For example, study Shannon's information theory connected with information transfer in noisy circuits (1948). Shannon's work links to Einsteinian physics. Suppose you are researching pharmacogenetics (biologically based). Study Shannon. DNA molecules encode and communicate genetic information including about inherited disease.

Less is more

Humans have the cognitive bias of attempting to improve something by complicating it. For example, drug A has a side effect; to reduce it, add drug B. However, the racing car designer Colin Chapman urged simplification and then adding lightness. His stressed monocoque racing car, the *Lotus* 25, was probably a first. Its simplicity is staggering. The principle is still used today; carbon fibre now provides lightness. Instead of adding a drug, why not use part of the patient? Today, we reseed idiopathically "sterilised" guts with a medicine containing quality-assured healthy stools from other people. Immune systems decline in potency with aging; healthy gut contents from a young person could be stored in liquid nitrogen and used to rejuvenate the gut microbiome

when later, that person becomes ill. Arguably, the pharmaceutical industry should become a pioneer in such expertise; otherwise, an organ transplantation/blood transfusion-type service might hijack. Legally they may use blue flashing lights for distribution. Would distribution using blue flashing lights benefit your company's image?

Do the opposite of your invention goal, method, hypothesis, or whatever. For example, as a natural scientist, you believe that samples *must* be random and sufficient for statistical testing. Instead, sample purposively. Select just a handful of cases having some specific rare characteristic that you have already decided. Social scientific (qualitative) research routinely uses purposive sampling. Purposively select, say *harmful* compounds. AI software was tasked (2022) to find toxic compounds; 40,000 were identified. They included all known chemical warfare compounds and some never before seen: terrifying. But you could convert such agents of death into life, informed by the ancient proverb, "The enemy of my enemy is my friend". So, theorise possible chemical "opposites" of the new compounds.

AI, by automating repetitive tasks, analysing vast datasets, and identifying complex patterns, can significantly accelerate the pace of discovery and innovation in engineering biology—and reduce the cost. AI can be used to design novel biological systems, predict the outcomes of genetic modifications and optimise drug development processes. You might invent pharmaceuticals that are beneficial to human health, perhaps even offering astounding benefits.

Ensuring responsible development and deployment of these technologies is crucial .

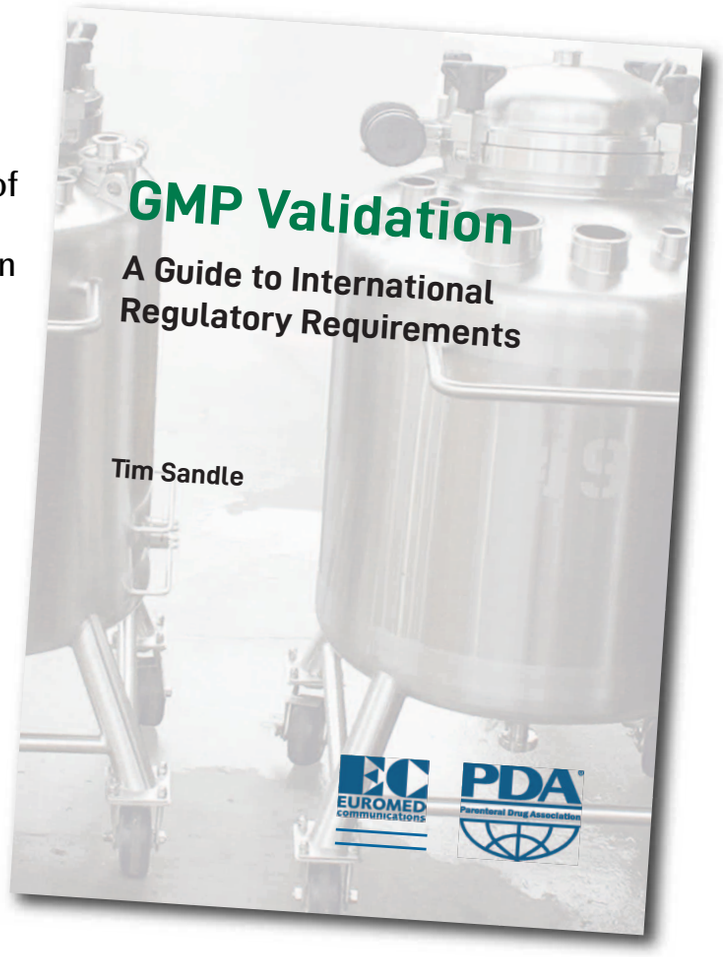
Research in pharmaceutical development often encounters significant hurdles. For instance, some promising therapies, such as phage therapy in Georgia since the 1920s, have been hindered by geopolitical factors or perceived as 'undruggable' due to challenges related to dosage forms, shelf-life, and profitability; David Browning (IP 2025; 74: 6-10) overviews a recent re-awakening of interest. The potential of cutting-edge AI in overcoming obstacles is being explored. AI may generate novel therapeutic approaches that lie outside the scope of human intuition, akin to AlphaGo's unexpected "Move 37" that confounded even the most skilled Go players. To harness their benefits while mitigating potential harms rigorous experimental validation in the real corporeal laboratory and clinical worlds are essential. When empirically synthesised, do so carefully. Extremely carefully. Self-aware ethical) humans must remain in the loop.

Malcolm E Brown

GMP Validation

A guide to international regulatory requirements

Tim Sandle



Within the pharmaceutical and healthcare sector, validation and qualification form an important part of the quality system. However, understanding the differences between different regulatory agencies and the recommendations of different standards can be a bewildering project. This new book seeks to provide a map and a compass for navigating the choppy waters of international regulations.

GMP Validation **provides a text for those who need to assess validation and ensure that validation is conducted according to current GMP. These include the validation manager and personnel engaged in validation activities; quality assurance; quality control; R&D; and production personnel.**
Some of the scientific aspects will also appeal to students, especially those working within or aspiring to enter the pharmaceutical sector. The book also serves as a good starting point for those who are tasked with auditing validation systems or items of equipment or processes.

This comprehensive handbook of 650 pages is comprised of 30 chapters which are divided into two parts. The first part is dedicated to the management process, with an emphasis upon appropriate formality and risk-based approaches. The second part focuses on case studies, providing an overview of different GMPs and standards for different areas of validation and qualification. The book concludes with four useful appendices providing templates to aid the reader.

Further information and ordering details can be found at:

https://euromedcommunications.com/collections/pharmaceutical-sciences-manuals/products/gmp-validation-a-guide-to-international-regulatory-requirements-1

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