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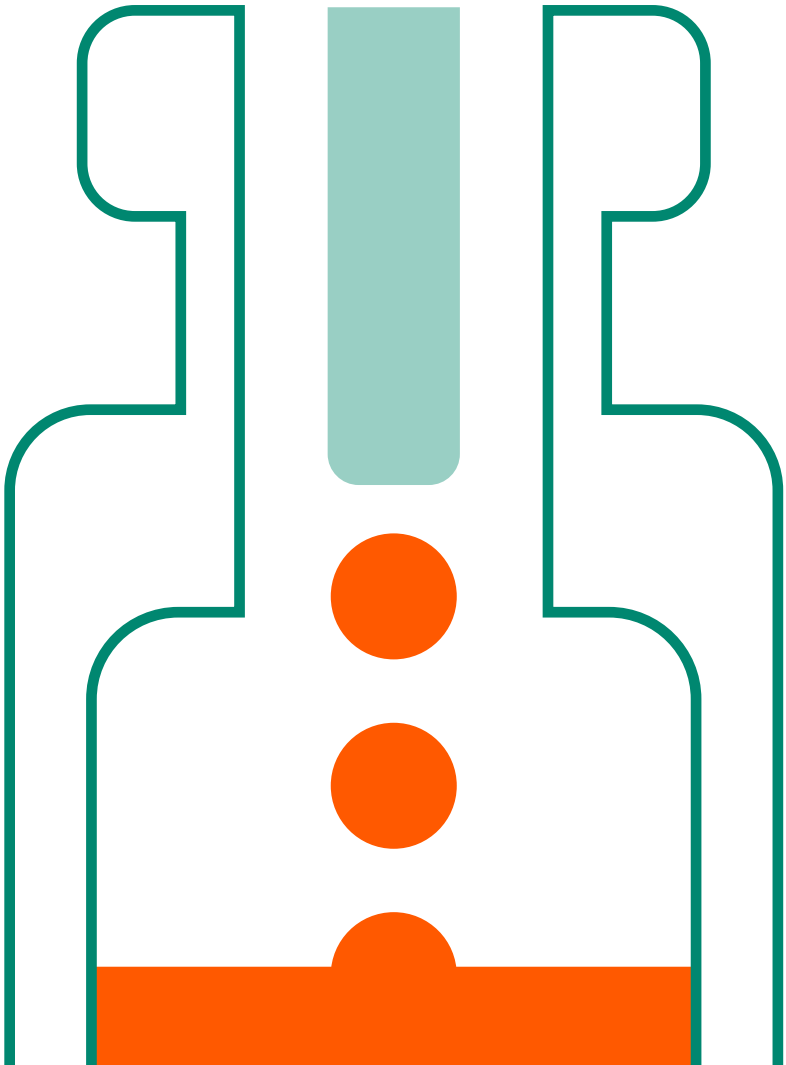

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Cost-effective, globally compliant aseptic filling solutions remain a challenge for drug manufacturers. Drug developers face mounting pressure to meet complex sterility regulations, especially for aseptic filling programs (1). The aseptic processing market is expected to surge from $99.5 billion in 2025 to a projected $189.8 billion by 2035 (6.7% CAGR). With more therapies entering global pipelines, staying ahead of diverse regulatory demands is crucial for maintaining a competitive edge.

Good manufacturing practices (GMP) regulations form the foundation of aseptic filling for injectable drug manufacturing. However, enforcement varies by region due to past contamination incidents and varying national healthcare priorities. Understanding regulatory differences regarding aseptic filling is essential, not just for compliance and contamination control, but also for risk management, patient safety, and market access. Discrepancies between regional requirements can delay product approvals, disrupt clinical trial execution, and strain supply chains. Without harmonization, market entry slows and costs rise, making early regulatory strategy a key driver of global success.

What strategies can manufacturers use to overcome these obstacles? It pays to know which aseptic filling methods have the potential to maximize return on investment, especially when seeking compliance across health authorities. While core principles like environmental monitoring (EM), aseptic process simulation (APS), gowning, process validation, and isolator use are universally recognized, specific regional interpretations may differ. To remain competitive, companies must think strategically to meet the demands of each market.

In this article, we explore how companies can implement adaptable and comprehensive aseptic filling strategies that maintain high quality standards while ensuring regulatory compliance across global health authorities. We also explore how well-documented, high-performing solutions such as robotic systems support compliance and how manufacturers can employ adaptable, regionally informed strategies for both global compliance and long-term competitiveness.

Regional health authorities

Each regulatory body's national priorities and history creates different requirements that global pharmaceutical companies must navigate. Western manufacturers often focus on US and EU regulations. However, companies conducting global trials or distributing products worldwide must also understand regulations in other regions, like Asia and the Pacific region (APAC), and those set by organizations like the World Health Organization (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

As WHO GMP Inspector Vimal Sachdeva explained in a 2024 ISPE Aseptic Regulatory Panel Q&A (2):

The revised Annex 1 (WHO TRS 1044, Annex 2) is the outcome of the joint work, which was done by the European Medicines Agency (EMA), PIC/S, and WHO. It is a classical example of a regulatory harmonization where three major regulatory authorities have decided to work together to have one common guideline for sterile pharmaceutical products.

Overall, we see that countries across the world are prioritizing harmonization. Still, manufacturers should note that some GMP regulations are yet to be harmonized. To illustrate these challenges, let's examine how different global health authorities approach GMP compliance.

Regional regulatory variance

EMA's Annex 1 is widely regarded as one of the more prescriptive sets of standards for aseptic processing. The 2023 Annex 1 wasn't only significantly expanded in length (58 pages compared to 16 pages from the 2008 version) but also introduced a new structure and in-depth coverage of any areas directly related to manufacturing sterile products (3). In greater detail, Annex 1 encourages the use of "appropriate technology", specifically mentioning isolators, restricted access barrier system (RABS), and robotic systems, demonstrating a growing acceptance of the favorability of these solutions as they pertain to sterility assurance and quality management.

Companies operating in the EU must make sure site inspections and documentation meet the expectations of both the EMA's Annex 1 and individual national agencies. Even considering Annex 1's prime place in the regulatory agenda, interpretations can vary across Europe, leading to country-specific enforcement differences. For example, while historically aligned with EMA, post-Brexit changes introduce additional documentation and compliance requirements, adding complexity for companies distributing in both the United Kingdom (UK) and the EU (4).

Prior to Brexit, the EMA played a central role in regulating and approving medicines across the EU, including the UK. However, with the UK's departure, the country's Medicines and Healthcare Products Regulatory Agency (MHRA) became a stand-alone body as it ceased to be part of

the European system of approval. This transition led to a series of challenges, including the need for pharmaceutical companies to duplicate their efforts by submitting separate pharmaceutical applications to both the EMA and MHRA for approval. Such nuances are important to bear in mind as regulatory uncertainty can lead to delays in approvals and increased costs for companies needing separate authorizations.

In North America, Health Canada and the US Federal Drug Agency (FDA) regulatory priorities for aseptic processing generally align. One notable difference being that Canada requires a drug establishment license (DEL) for each site involved in aseptic processing, while the US focuses on facility registration and inspection (5). However, Health Canada's approach is largely compatible with international standards, facilitating global harmonization but with some procedural and administrative distinctions.

In contrast, APAC consists of multiple countries with distinct, ununified regulatory priorities. For instance, although Japan's regulations are broadly aligned with EU GMP standards, the country places additional emphasis on quality control. Under the Japanese GMP drug standards, quality assurance entails a comprehensive system of procedures and processes aimed at ensuring the consistent production and control of pharmaceutical products to the standards appropriate for their intended use (6). As a result, manufacturers must adapt their quality systems to meet the specific expectations of Japan's Pharmaceuticals and Medical Devices Agency (PMDA), including adjustments to data integrity protocols, in-process controls, and batch release procedures.

In Singapore, supply chain resilience takes center stage. In a country known for a strong emphasis on continuity and security, the country's regulations require companies to demonstrate robust logistics and contingency plans. In addition to the mandatory product registration, companies involved in the pharmaceutical supply chain may also need to obtain one or more licenses, depending on their specific business activities (7). While Singapore's alignment with global standards facilitates approvals, companies should be prepared to provide additional documentation detailing their supply chain risk mitigation strategies.

India is continually refining its regulatory frameworks, presenting an ongoing challenge for manufacturers working within strict timelines. In response to high-profile drug contamination scandals, Indian authorities have increased oversight and inspection frequency – particularly for companies exporting to the US and EU (8). To remain compliant, manufacturers must demonstrate enhanced quality control measures that meet the evolving expectations of the Indian Pharmaceutical Alliance (IPA) and the Central Drugs Standard Control Organization (CDSCO), India's national regulator.

Similarly, in China, regulatory requirements shift rapidly in response to both domestic priorities and international developments. For manufacturers, this creates a moving target where compliance strategies and documentation must be continuously updated to meet the National Medical Products Administration's (NMPA) expectations.

In March 2025, the NMPA published a draft regarding new GMP requirements for sterile medicinal products (9). These updated aseptic processing requirements focus on contamination control strategies (CCS) and the implementation of advanced barrier concepts such as isolators and RABS. Mirroring the EU's revised Annex 1 (2023), NMPA guidelines emphasize sterility assurance and technological modernization. To comply, manufacturers must be proactive; failure to keep up with such changes can lead to supply chain delays and regulatory setbacks.

While regulatory harmonization remains the goal — and important steps have been taken in that direction — differences in education, awareness, and economic resources continue to pose challenges for manufacturers operating across diverse regions.

Many developing nations still rely on WHO and International Organization for Standardization (ISO) manufacturing guidelines rather than maintaining comprehensive, standalone GMP frameworks. Encouragingly, initiatives like WHO TRS 1044, Annex 2 are helping to promote greater consistency and shared understanding among global health authorities.

However, pharmaceutical companies operating in emerging markets must still navigate localized adaptations of these guidelines, which may diverge from western regulatory expectations. This makes alignment more complex, even in a progressively harmonized landscape.

GMP manufacturing across health authorities

How can you design a global aseptic filling strategy when each major regulator defines 'best practices' differently? Understanding how regulatory agencies differ in their aseptic processing requirements is the key to avoiding delays, reducing compliance risks, and designing a scalable, future-proof strategy for clinical trials and commercial distribution.

This section breaks down some of the more critical regulatory differences and offers practical steps to help manufacturers operate as seamlessly as possible across global health authorities.

Environmental monitoring (EM)

Variability in EM standards impacts contamination control strategies, leading to different compliance burdens depending on the region. A lack of global standardization increases the risk of failed inspections in one region despite acceptance of the same EM practices in another.

Limited funding outside North America and Europe often restricts exposure to advanced EM technologies, such as biofluorescent particle counters (BFPCs). However, increasing quality standards are driving growing interest in real-time monitoring with BFPCs across APAC signaling a potential shift. For now, though, most regions continue to rely on traditional, less timely EM methods like settle plates.

Settle plates, although an established method, aren't equally respected by all regulators. Generally, they are considered to be of less value by inspectors from the United States compared with Europe (10). A major reason that the FDA finds settle plates to be an inferior EM strategy is their semiquantitative nature. Additionally, their results can be influenced by their placement and the duration of exposure while they are only able to detect particles that settle by gravity, missing those carried by airflow.

The FDA and EMA align on the use of isolators with unidirectional airflow and real-time monitoring via technologies like BFPCs that support both vertical and horizontal capture. While Annex 1 promotes high-tech solutions, regulators increasingly recognize the need for scalable, risk-based approaches – particularly in developing markets where infrastructure and capital investment may be constrained.

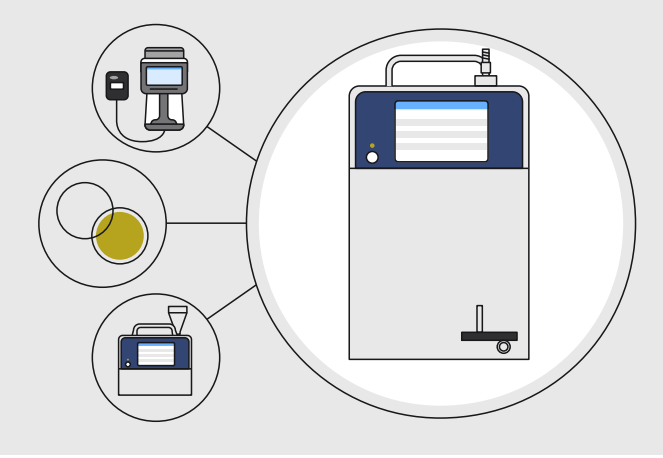

Fig 1. Biofluorescent particle counters, such as TSI's BioTrak™ Real-Time Viable Particle Counter, combine traditional methods such as active air sampling, total particulate counting, and settle plate technology to advance environmental monitoring and provide real-time insights in aseptic filling.

Aseptic process simulations (APS)

Global companies must design APS strategies that satisfy multiple regulators, despite regional differences in media fill frequency, contamination limits, and revalidation triggers. Varying contamination limits (for example Annex 1's zero growth limits vs. the FDA's investigation thresholds) mean companies may pass APS in one region but fail in another, complicating regulatory filings. Therefore, it is important that companies aim to comply with the most stringent contamination requirements and thresholds.
While most countries' alignment with the EMA's Annex 1 makes this seem simple in concept, differences in validation and revalidation schedules and differing approaches to process integration make this a challenge. The FDA and EMA both expect manufacturers to use documented risk assessments to determine the types and frequencies of interventions to be simulated, ensuring that worst-case scenarios are covered.

In contrast, The IPA lists "closing media fills" after process modifications or facility shutdowns as part of their best practices (11). This involves performing media fills before major changes or after extended inactivity so that sterility assurance isn't compromised.

These additional requirements increase the compliance workload for manufacturers, as they must frequently validate processes and conduct media fills under varied conditions, including worst-case scenarios and major operational changes.

An example of a non-negotiable regulatory hurdle is Japan's enforcement of strict requirements linking heating, ventilation, and air conditioning (HVAC) performance to APS outcomes. This includes establishing a program for HVAC system maintenance and environmental monitoring.

It's critical to ensure with respect to temporal variations caused by operational activities, such as door openings, closings, and equipment operation. APS should also account for sustained variations resulting from non-operational factors, such as seasonal changes in outdoor conditions or the gradual deterioration of equipment and apparatus over time.

Any modification to the HVAC system automatically triggers APS revalidation to reconfirm sterility assurance. This tightly coupled approach demands a detail-oriented and often more burdensome bureaucratic process due to Japan's stricter documentation requirements, including (12):

- Detailed correlation between specific HVAC parameters (e.g., pressure differentials) and APS outcomes.
- Real-time HVAC monitoring during media fills, with deviations directly tied to environmental monitoring records.

To help meet these elevated standards, manufacturers are relying more on robotic systems, which offer precise control, minimize human intervention, and reduce the risk of contamination during aseptic fills.

Gowning requirements

Sometimes, even North America and the EU differ in their regulatory priorities, as in the case of gowning requirements for Grade A/B environments. The EU mandates sterile, non particle-shedding garments, including two pairs of sterile gloves, sterile headgear, face masks, goggles, and boots (13). All skin and hair must be fully covered to prevent contamination, and operators must follow progressive gowning procedures when moving from less clean areas into Grade A/B zones.

The US also requires sterile garments but places greater emphasis on GMP donning and doffing procedures to reduce contamination risks (14). Training and certification are essential to meet this focus, but progressive gowning steps are often not as extensive as in EU GMP. Training and reassessment frequency is also less rigidly specified in North America than in the EU guidelines. Manufacturers distributing in both the EU and US must balance gowning requirements and compliance techniques for both regions.

In other regions, gowning regulations are often based on localized climate and infrastructure, meaning multinational facilities must account for differing heat stress risks and material compatibility. Common industry practice is to provide lower environmental temperatures as the level of gowning increases (15).

Failure to meet region-specific gowning expectations could result in regulatory setbacks, even if aseptic practices remain unchanged. By eliminating the need for human presence in the filling chamber, automated robotic isolators not only streamline operations but also offer a decisive solution to the regulatory complexities of gowning compliance.

Contamination control strategy (CCS)

Advancements in aseptic filling—such as closed systems, isolators, and automated environmental monitoring—are reshaping CCS across the industry (16). These innovations not only improve operational efficiency and product quality, but also align closely with evolving global regulatory expectations.

However, inconsistency among health authorities remains a major frustration for manufacturers. While many strive to implement the latest technology, the lack of harmonized requirements makes global compliance a moving target.

If we envision this situation as a spectrum, the EU sits at one end, pushing aggressively toward automation, real-time environmental monitoring, and data-driven CCS (16). At the opposite end are countries with less mature regulatory frameworks, where traditional EM methods and manual processes still dominate.

In this context, robotic systems stand out: they are thoroughly documented, minimize human intervention, and meet high standards for contamination control, making them "future-proof" as regulations converge.

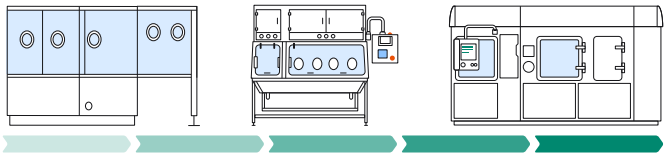

Fig 2. The evolution of aseptic filling technologies to support CCS.

Isolators vs. open cleanrooms

Similar to CCS, cleanroom practices vary substantially across regions. Western regulatory bodies — including the FDA and EMA — strongly favor isolators and automated systems. In fact, the EU's Annex 1 strongly recommends using advanced barrier technologies such as isolators and RABS to eliminate human intervention in Grade A zones.

The impact of different regulatory interpretations on companies that operate in multiple regions

A 2024 survey published by the Parenteral Drug Association (PDA) Journal of Pharmaceutical Science and Technology reported that conflicting interpretations among health authorities and inspectors lead to increased costs and potential delays with over 50% of the survey respondents reporting conflicting interpretations, particularly for CCS, barrier technologies, and APS requirements (17). These inconsistencies force companies to adopt different approaches or invest more to meet various regulatory expectations, which increases costs and potential delays.

Furthermore, the delays and cost increases associated with Annex 1 compliance were less a result of staggered implementation, and more a reflection of delayed planning and investment decisions. Although certain requirements — such as those for lyophilizer loading/unloading — came into force later than others, the overall revision process began as early as 2017, with draft guidance and regulatory conversations already signaling the direction of change. However, many companies chose not to act until the final version was published, despite having early opportunities to align with evolving expectations. This resulted in approximately 40% of participants needing a time extension

beyond August 2023 for full Annex 1 compliance, with CCS and barrier technologies identified as the top lagging areas. These findings suggest that organizations that delayed proactive improvements faced greater challenges meeting the regulatory deadlines.

Regulatory complexity is a hurdle that can't be overlooked

Differences in regulatory expectations create barriers to efficiency, forcing manufacturers to navigate multiple sets of requirements. Many global manufacturers are already overcoming these challenges by investing in real-time EM, automation, and strong regulatory collaboration for their aseptic filling processes.

With regulators emphasizing contamination control and sterility assurance, automated filling and isolator-based systems are increasingly favored. However, regional differences in automation acceptance mean manufacturers must balance regulatory requirements while adopting flexible, scalable technologies to remain compliant worldwide.

Rather than a one-size-fits-all compliance model, companies can gain a competitive advantage in multiple regions by developing flexible compliance strategies. This adaptability not only supports faster approvals and uninterrupted market access – it also enables a more agile response to shifting global health needs.

While manufacturers must adapt, regulators also have a role to play. Fragmented regulations create inefficiencies that slow down drug availability and hinder innovation. Greater global regulatory harmonization — such as initiatives like ICH Q12 for post-approval changes — can lower barriers to trade, improve supply chain flexibility, and support broader access to critical medicines.

Regulatory landscapes will continue to evolve as agencies respond to technological advancements, supply chain risks, and public health priorities. Despite the complexities, the future of aseptic processing is bright. Companies that proactively embrace advanced technologies and foster regulatory alignment will be well-positioned to meet global demand.

Cytiva is your helping hand for aseptic filling of pharmaceuticals. With scalable systems like the Microcell™ vial filler and the SA25 aseptic filling workcell already in use worldwide, our technologies position you at the forefront of compliance and future-ready manufacturing. Contact us today to learn how our products and services can streamline your international regulatory applications.

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