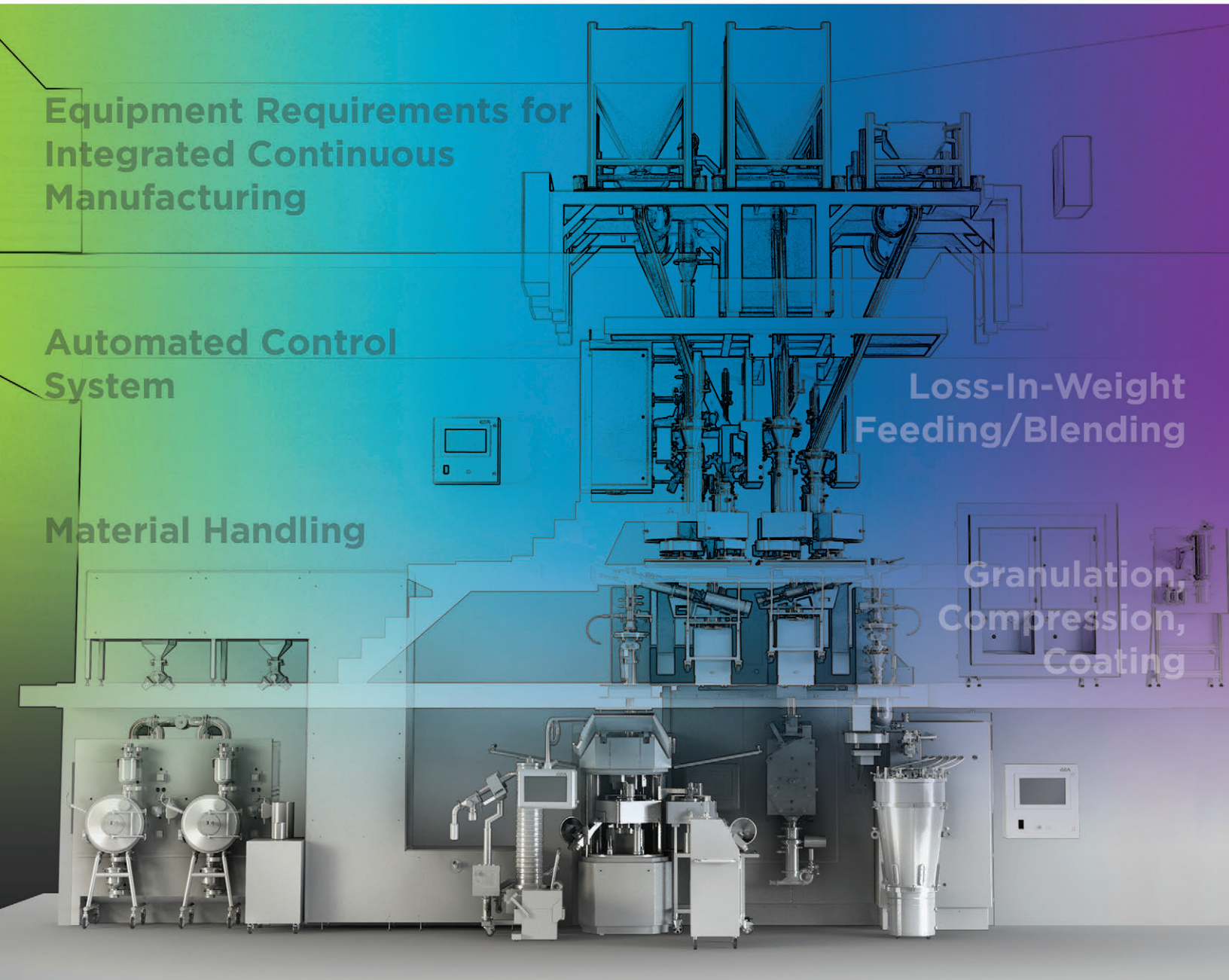
ISPE®

GOOD PRACTICE GUIDE:

Continuous Manufacturing of Oral Solid Dosage Forms



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Preface

The pharmaceutical industry has begun to embrace Continuous Manufacturing (CM) technologies to develop and commercialize both new and legacy products. While there continues to be significant production executed routinely and acceptably under the traditional batch paradigm, the application of continuous manufacturing principles and equipment to pharmaceutical processing can lead to decreased costs and time in development as well as robust assurance of final product quality for manufacturers.

This Good Practice Guide reviews the major drug product unit operations typically employed in continuous manufacturing and aims to establish a set of minimum equipment requirements for each type of system to function as part of an integrated process train. Although most of the unit operations discussed are already well-understood and utilized in batch manufacturing (the notable exceptions being loss-in-weight feeding and continuous blending), the physical and automation requirements for all equipment to work in concert as part of a successful continuous manufacturing platform need to be carefully considered. This Guide can be utilized as a companion reference to the *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [1] by pharmaceutical companies looking to deploy new continuous manufacturing technology, as well as by vendors and end-users focused on designing the next generation of continuous manufacturing systems.

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1 Introduction

Starting in the mid-2000s, the pharmaceutical industry began to apply the principles of continuous processing to the manufacture of Oral Solid Dosage (OSD) medicines. While the industry initially focused on establishing the technical capabilities of continuous manufacturing systems, it has now advanced to the commercial manufacture of multiple drug products with distribution approved in the US, Europe, and other countries around the globe.

The consensus among experienced practitioners is that the continuous approach has numerous benefits. It is often more robust than its batch counterpart, it is designed for reduced variability, and it can achieve improved product quality through better blend uniformity. These features can be especially beneficial in the case of drugs with a narrow therapeutic index. In addition, continuous manufacturing offers potential safety benefits such as lower exposure risk for operating personnel.

Moreover, the same attributes of continuous manufacturing that make it technically favorable have long been predicted to make it economically advantageous [2]. This leaves the industry in a non-ideal state, where few people question the merits of the approach but many challenges to widespread adoption remain.

The following four conditions are recognized as fundamental business challenges for continuous manufacturing:

- CM lines are capital intensive, often costing US$10–30 million (€9–27 million).
- CM lines involve complex automation that require significant validation effort in addition to the validation of the physical equipment comprising the various unit operations.
- CM lines are capable of producing large scale quantities (0.5–3 billion units per year), but the average product volume of new drugs in development is in the low 100s of millions of units, which does not require high-throughput plants.
- Fully integrated CM lines require different operator skill sets than are currently available, typically including higher levels of automation and process understanding.

While some organizations may have a small number of very high volume products for which a dedicated continuous line could be built, most companies are discovering that in order to justify the cost of the technology, continuous manufacturing lines need to be multi-product capable and rapidly deployable. Given the wide range of variability of pharmaceutical product profiles (e.g., dose, weight, volume, number of components, raw material handling needs), a line with a fixed design is highly likely to be incompatible or suboptimal for the breadth of products in an organization's portfolio. If the line cannot sustain a high rate of utilization, the positive economic benefits of continuous manufacturing may not be realized. The technical skills required to design and deploy a customized flexible build are also a challenge for many pharmaceutical companies above the investment in the machinery itself. Therefore, the time investment before a return on investment is achieved also becomes a limiting factor.

It is evident that for continuous manufacturing to achieve its full potential, a different approach to process engineering, system design, and operation is imperative without compromising the robustness required for manufacturing in a Good Manufacturing Practice (GMP) environment. As more companies integrate continuous manufacturing into their development and commercial operations, there will inevitably be an increased demand for more flexible, modular, and robust systems that can accommodate a wider range of products and production control strategies. This Guide provides a valuable resource for new and existing companies as they design and integrate continuous processing equipment into their operations, highlighting best practices and opportunities for enhancement to both vendors and end-users already engaged in developing continuous manufacturing lines of the future.