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Making parenteral medication safer.

Accuracy in practice

Realistic boundaries and optimisation through automation

From manual compounding to automated precision – a nuanced perspective

1 Introduction

Manual preparation of sterile medications remains the gold standard in many hospital pharmacies. Pharmacists rely on a set of processes and tools – from syringes and drug vials to IV bags – that each contribute to the quality of the final product. At the same time, it is an open secret that these processes inevitably introduce inaccuracies. In this whitepaper, we examine the nature of these inaccuracies, clarify the role of gravimetric control, and put the capabilities of automated systems – such as The Compounder – into perspective. Not as a miracle solution, but as a tool to implement realistic improvements in a system that, until now, has been largely based on manual handling.

2 The reality of inaccuracy in manual preparation

While manual preparation is widely practiced and deeply embedded in daily routines, there are various sources of variability that structurally affect accuracy. This variability arises not only from the act itself but also from the tools and drugs used.

2.1 Inaccuracy in syringes

- **Graduation and ISO standards**: According to ISO 7886-1:2017[1], syringes ≥ 5 mL may deviate by ± 4% when used at ≥ 50% of their capacity. For smaller volumes (e.g. 0.1 mL in a 1 mL syringe), deviation can rise to ±16%. For example, a target dose of 50 mL in a 50 mL syringe may actually be between 48 and 52 mL, even when filled exactly to the mark.
- **Diameter variation**: Plastic syringes have manufacturing tolerances in internal diameter, directly affecting the volume displaced per plunger movement. For a full stroke intended to displace 50 mL, this results in:

BD Plastipak 50 mL[2] (26.59 mm ± 0.13 mm):	Min. diameter (26.46 mm): ~ 48.5 mL Max. diameter (26.72 mm): ~ 51.1 mL Range: ± 2.6%
B.Braun Omnifix 50 mL[3] (28.00 mm ± 0.1 mm):	Min. diameter (27.90 mm): ~ 48.6 mL Max. diameter (28.10 mm): ~ 51.4 mL Range: ± 2.8%

- **Reading errors**: Reading volumes between scale marks is prone to error and often discouraged in pharmacy practice – yet still frequently observed. Even reading directly at a marked line is challenging: interpretation depends on viewing angle, lighting, and print accuracy. This results in considerable variability, particularly at smaller volumes.

2.2 Inaccuracy in medications

- **Label claims**: A 1 mL ampoule labelled 100 mg/mL appears exact, but is subject to tolerances. Extra volume is often included to meet extractable volume requirements. Furthermore, EU regulation requires that a medication's content at the end of its shelf life must lie between 90% and 110% of the declared strength. Thus, both the volume and concentration carry permitted variability.
- **Reconstitution brings additional variability**: When powders are dissolved, the volume of diluent added introduces further uncertainty. In practice, the added volume is typically approximate, resulting in variation in the final solution's concentration.

2.3 Inaccuracy in IV bags

- **IV bag overfill**: IV bags are consistently overfilled. This overfill is not precisely predictable and contributes to variability in final concentration after preparation.

2.4 Tolerance stacking

All these factors accumulate. This phenomenon – known as 'tolerance stacking' – leads to final dosages that may deviate significantly from the intended dose, often exceeding ± 10-20%, without being visibly apparent. This is clearly illustrated in Dennis Tribble's essay The Illusion of Accuracy[4], where concrete examples show how daily practice often aims for a level of precision that is unattainable in praxis due to inherent tool and process limitations.

3 The role and limits of gravimetric control

To better manage variability, gravimetric control is increasingly used. Based on known density and transported volume, an expected weight change is calculated and compared to the measured weight on the scale. While valuable, this method also has limitations.

- **Scale accuracy**: Scale deviation is not a fixed percentage and depends on range, resolution, and stability. (See the separate whitepaper on weighing accuracy for a detailed explanation.)
- **Density as approximation**: Density is often treated as a constant, but is in fact a range. Most medication solutions contain excipients (e.g. NaCl for osmolarity), so the active ingredient typically contributes little to the total density.

Gravimetry therefore primarily confirms that a mass was transferred within acceptable margins. While it does not provide absolute certainty, it is significantly more reliable than visual measurement.

4 What can you expect from automation?

When automation systems such as The Compounder[5] are used, tighter accuracy limits are often set, e.g. 97-103%. While logical, this contrasts sharply with the broader variation in manual processes. It is therefore essential to put such expectations in context.
The Compounder uses commercially available 50 mL syringes from brands like BD Plastipak and B. Braun Omnifix. Both the plunger and flanges are mechanically fixed to avoid positioning variation. However, the syringes themselves remain subject to the tolerances mentioned earlier.

4.1 Actuation and precision

The Compounder uses a stepper motor with encoder, capable of actuating the plunger in steps of 0.09 mm. This allows the plunger height to be set with high precision and reproducibility. Combined with the pre-entered syringe diameter, this enables highly accurate volume approximation. This high level of positional control means that the plunger movement itself contributes minimally to variability. Nevertheless, certain influencing factors persist, originating from the syringes' mechanical properties:

- **Cylindrical deformation** under pressure during aspiration or dispensing
- **Elastic compression or expansion of the plunger** under resistance
- **Friction between plunger and barrel,** which may cause slipping or rebound

These effects are usually small, but not negligible. The Compounder therefore significantly reduces variability from manual handling but, like any system, is still subject to the limitations of its components. The achieved accuracy falls within pharmacologically acceptable tolerances and is particularly reproducible, controllable, and suitable for standardisation in critical compounding environments.

5 Conclusion

Sterile medication preparation has never been perfectly exact – and never will be. But with a solid understanding of variability sources and the effective use of technologies such as gravimetry and automation, we can manage and reduce that variability. The Compounder introduces a new standard: not by claiming perfection, but by placing transparency, reproducibility, and realistic control at the core of the compounding process.

References

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