

Bioprocessing

Successful manufacturing of dry powder media from development to large-scale cGMP production

A two-phase strategy to deliver rapid prototype material and help sustain quality with scale-up

Situation

Bioprocessing risks and challenges exist in maintaining quality and equivalency in custom cell culture media between the creation of non-GMP prototype material and its scale-up/formulation transfer to current good manufacturing practice (cGMP) production. Here we outline the process and results of a two-phase scale-up strategy that was used for three complex dry powder medium (DPM) projects. The success of these projects relied on consistently producing acceptable prototype and cGMP material within the customer's specifications and manufacturing timelines.

Solution

A two-phase strategy was employed. The first phase was conducted upon transfer of the customer formulations to Gibco™ Rapid Prototyping Services (GRP) at the Hunt Valley, Maryland, or Grand Island, New York, sites. During this phase, GRP team members evaluated and consulted with the customer regarding any potential manufacturability issues. Subsequently, several initial non-cGMP-scale lots were produced and tested. The second phase involved internal technology transfer and scale-up with the production and testing of several larger-scale lots with cGMP Media Manufacturing Services at the Miami, Florida, or Grand Island, New York, sites. Lastly, the test results from the GRP and cGMP production of DPM were evaluated for equivalency of scale-up from GRP to cGMP. The three DPM formulations are referred to as DPM1, DPM2, and DPM3.

- DPM1 and DPM2 formulations were transferred with three initial 5 kg lots produced in the GRP facility. Standard GRP testing for these lots included pH and osmolality, with additional analytical testing added for bioburden, endotoxin, glucose, salts, amino acids, water-soluble vitamins, and trace metals.* For added assurance, the customer requested that three additional GRP lots be produced for critical analyte group testing: amino acids, water-soluble vitamins, and trace

metals. Upon customer approval of the material from the GRP facility, five larger 38–56 kg lots were produced and tested at the cGMP facility. (See Table 1 for GRP and cGMP manufacturing capabilities for DPM.)

- DPM3 was initially manufactured and tested at the GRP facility with two 5 kg lots. Once determined acceptable, it was transferred and manufactured at the cGMP facility with two 2,500 kg lots. GRP and cGMP facility lots were tested for pH, osmolality, bioburden, endotoxin, glucose, salts, amino acids, water-soluble vitamins, and trace metals.

* Analytical testing of GRP products is available for additional fees.

Table 1. Gibco DPM manufacturing capabilities.

Facility type	Batch sizes*	Approximate turnaround time
GRP	1–30 kg	2 weeks
cGMP	10–10,000 kg	12–16 weeks

* Batch sizes are dependent on manufacturing site and based on bulk density/production suite.

Results

Overall, the comparative GRP to cGMP test analyses showed acceptable component group-level equivalency from small-scale to larger-scale cGMP productions. The DPM1, DPM2, and DPM3 test results for bioburden, endotoxin, and individual analytes were within the established specification ranges (data not shown). Results at the component group level are reported herein to maintain formulation confidentiality. However, customers receive detailed results of each individual component level. Typical acceptable variability ranges up to $\pm 20\%$ for most customers. (Ensuring lower variability, within $\pm 10\%$, may require additional production lots.)

- GRP to cGMP analyses of the test results of DPM1 and DPM2 demonstrated relative average component group agreement of 100% for pH, 98–100% for osmolality, 103% for 14 quantifiable amino acids, 108–109% for six quantifiable vitamins, and 105–111% for five quantifiable trace metals (Figure 1A, 1B).
- Similar comparative GRP to cGMP analyses of DPM3 relative average component groups showed 100% comparability for pH and osmolality, 101% for 18 quantifiable amino acids, 102% for six quantifiable vitamins, and 97% for four quantifiable trace metals (Figure 1C).

Summary

Utilizing a two-phase, multiple-lot strategy can help deliver the required rapid prototype material and data analyses needed to ensure that consistent product quality is maintained from development or transfer through scale-up to cGMP.

The success of this two-phase, multiple-lot strategy is further supported by:

- Detailed formulation batch records and well-established technology transfer processes
- Harmonization and common sourcing of GRP and cGMP-qualified raw materials
- Use of identical or equivalent GRP and cGMP equipment design and manufacturers
- Robust raw material and quality control systems
- Control and quality systems in place with sites
- Site-to-site manufacturing comparability from well-established site and equipment validation processes

Bioproduction manufacturers are more likely to experience better success with the timely development and scale-up of custom DPM media formulations when the manufacturing supplier is consulted as early as possible in the development or CMO search process.

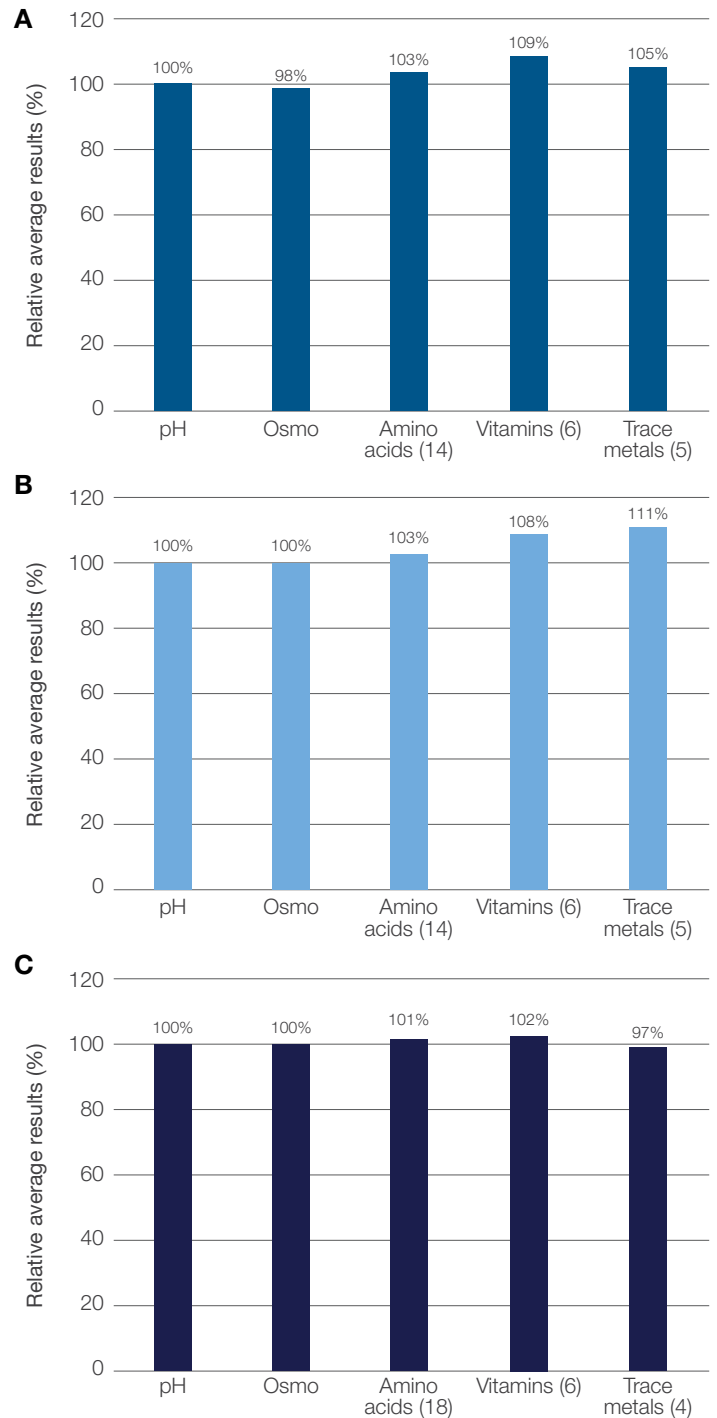


Figure 1. Relative comparability of analytical results from GRP to cGMP. (A) DPM1 component group test results, (B) DPM2 component group test results, and (C) DPM3 component group test results. Numbers in parentheses denote the number of individual quantifiable analytes in each component group.