SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Irvine Dry Powder Media Facility

Validation Harmonization

Introduction

The Dry Powder Media (DPM) manufacturing facility of Merck KGaA Darmstadt, Germany located in Irvine, Scotland completes a Capital Expansion Plan initiated as part of its long-term commitment to supporting customers in the growing industrial biopharmaceutical market. The purpose-built facility produces animal component free (ACF) media and offers regional support to the European market along with manufacturing redundancy to its North American sister facility in Lenexa, Kansas.

The purpose of this document is to present details of the validation strategy for the new facility and an overview of the harmonization approach to ensure comparability with the Lenexa plant. This document helps explain the performance qualification (PQ) approach behind this new facility.

While there are no specific regulatory requirements which apply to the manufacture of dry powder cell culture media, it was our intent to fulfill industry expectations in compliance with the relevant US FDA and EU legislation governing cGMP biopharmaceutical production to the extent appropriate to ensure product consistently meets specification. An overview of the regulatory references used can be found in the Validation Approach section of this document.

The completed validation package provides a high degree of assurance that the Irvine DPM facility can consistently produce product across the required operating range in accordance with documented User Requirement Specifications, Finished Product Specifications and customer expectations of GMP compliance. The validation package demonstrates equivalence of product with that produced at the existing Lenexa facility.

Facility Design Overview

The Irvine, Scotland DPM facility is designed for the validation, manufacture and packaging of ACF dry powder media batches from 25 - 6000kg. The facility includes:

- New raw material and finished goods warehousing with temperature mapped and controlled storage areas that are continuously monitored via a new Facility Monitoring System (FMS).
- New formulation suites to support product lot formulation from small to large scale. Formulation rooms are designed with humidity control and continuously monitored.
- Two separate manufacturing lines

Line 1	
Mill Type:	Pin Mill
Pre-Blender:	Conical, Auger Screw Blender
Post- Blender:	Tumble
Batch Size:	750-6000KG

Line 2	
Mill Type:	Pin Mill
Pre-Blender:	Tumble Blender (IBC)
Post-Blender:	Tumble Blender (IBC)
Batch Size:	25-750KG

The tumble blenders in Line 2 operate with 200L, 1000L or 2100L IBC's

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We have many years of experience working with equivalent blending and milling technologies in our global operations.

- Process rooms are supplied by dedicated HVAC systems where appropriate, environmentally controlled and monitored via the FMS.
- Validated cleaning processes for all equipment including Clean-In-Place (CIP) processes for fixed equipment and pipework, Clean-Out-Of-Place (COP) wash room and an automated IBC washer.
  All cleaning processes utilize industry recognized CIP-100® and include a purified water final rinse followed with a defined drying cycle.
- New Purified Water (PW) plant and distribution loop producing EP/USP grade PW
- Clean compressed air and clean nitrogen supply and distribution.

Validation Approach

All validation work was carried out in accordance with recognized standards and guidance for the validation of the new facility. This included Good Manufacturing Practice as defined in 21 CFR Parts 210 and 211, 21 CFR Part 11, EU Orange Guide, GAMP 5 and ISPE guidance on utilities, commissioning and qualification. These references are fully defined within the Irvine DPM Facility Validation Master Plan (V12-303-VMP).

Engineering studies were carried out as a precursor to formal qualification. These studies were used to develop the key process parameters that were used during performance qualification (PQ).

Due to the level of flexibility required by the DPM facility, it was not possible to exhaustively test the entire range of products and operational parameters. Qualification has therefore been designed using a risk based approach to define a range representative of routine use, for example using representative products and maximum/minimum operating parameters. High level details of the validation strategies for key activities are presented within this document.

Equipment Qualification

Equipment design and qualification followed the principles outlined in recognized industry guidance documents, for example the ISPE baseline® guides. All equipment was qualified to demonstrate compliance with approved User Requirement Specifications.

The facility was broken down into systems to facilitate qualification. Each system and component were subject to an impact assessment to determine criticality. Criticality was defined based on potential impact on product quality using the designations of direct, indirect and no impact. The level of qualification testing required was determined based on these assessments.

Direct impact systems were subject to formal design review, installation qualification (IQ) and operational qualification (OQ). Factory acceptance testing (FAT) and site acceptance testing (SAT) were carried out on major items of equipment where appropriate. Critical control systems were validated based on current GAMP guidance. All systems were subject to Good Engineering Practice.

This strategy is consistent with the approach used at the Lenexa facility.

Details pertaining to the PQ of critical systems are outlined below.

Process Validation

The process validation strategy for the Irvine facility is a matrix based approach consistent to that of the Lenexa site and designed to comprehensively support the increased level of flexibility required for the facility. A matrix which brackets batch volume and representative media in each production line has been developed as the basis for validation. Successful process validation of these products were referenced to support all products planned for transfer from the Lenexa to Irvine site. A minimum of three batches were produced on each of the two production lines (Line 1 and Line 2) to demonstrate consistency and reproducibility.

1. **Scale:** Validation of multiple media manufactured across a variety of production scale including minimum and maximum lot sizes (25 – 6000kg). A minimum of three lots were produced on each manufacturing line to demonstrate consistency and reproducibility.

   It should be noted that Line 2 pre and post blenders can be operated with one of three IBC sizes (200L, 1000L, and 2100L). Four blender combinations have been selected for manufacture, each were validated at maximum and minimum lot size resulting in 8 PQ batches, refer chart 1.

2. **Product Manufacturing Categories:** The process validation was carried out using a bracketing strategy with products having a known manufacturing history and considered representative of a worst-case manufacturing scenario for each group. Our Research and Development (R&D) team performed a technical assessment which included (but was not limited to) formulation type, raw materials interactions and milling characteristics. Multiple products were selected to represent one of three major media manufacturing categories:

   a. Classical

   b. Complex Chemically-defined

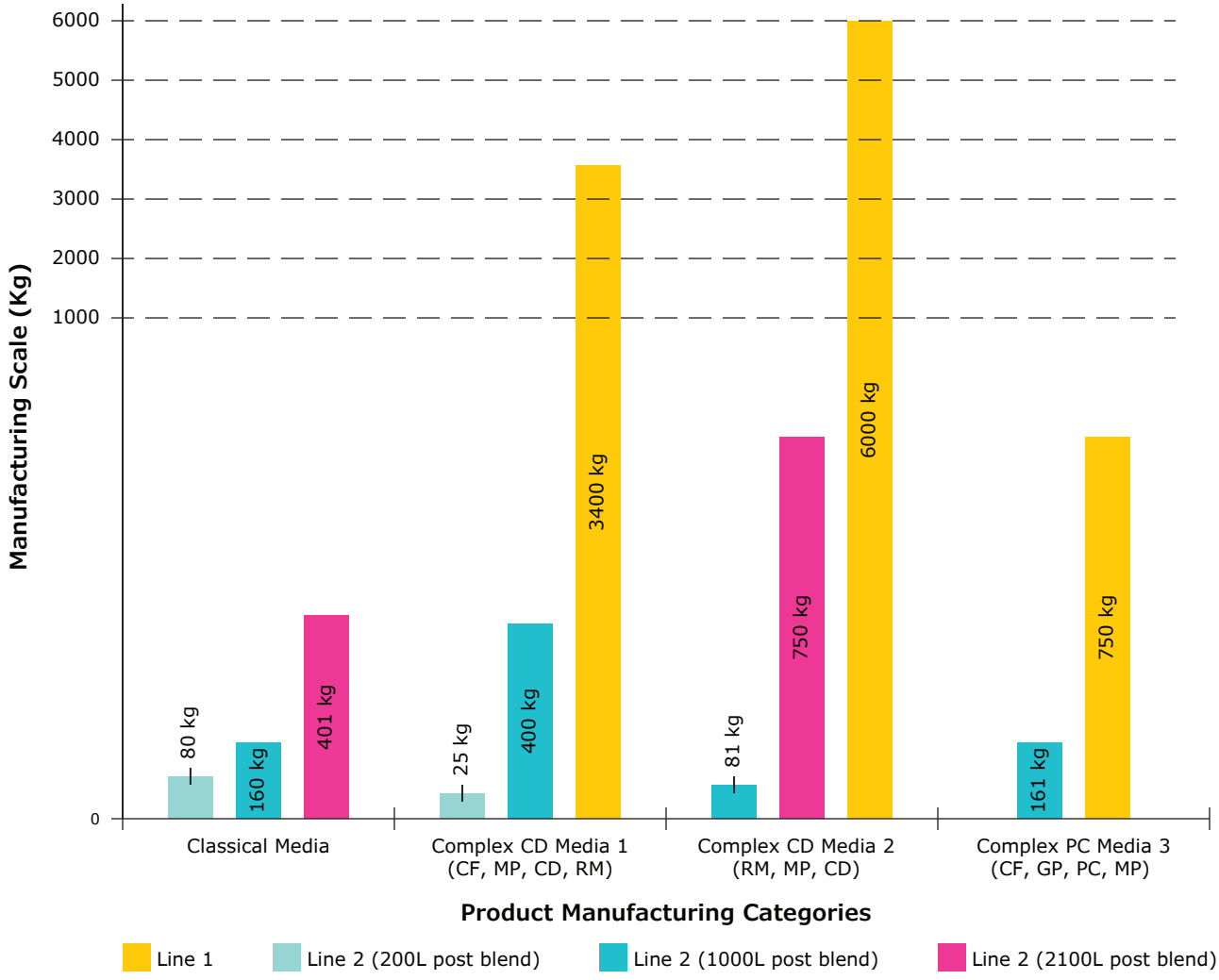
   c. Complex Protein-containing

Table 1. Process Challenges by Media Category

Media Category	Specific Process Challenges	Number of Lots
Classical	Raw material interaction presenting milling challenge (RM)	3
	Low melting point raw materials presenting milling challenge (MP)	
	Growth promotion test as measure of manufacturing success (GP)	
Complex Chemically-defined	Chemically defined (CD)	6
	Raw material interaction presenting milling challenge (RM)	
	Complex formulation subgroups providing additional manufacturing challenge (CF)	
	Low melting point raw materials presenting milling challenge (MP)	
Complex Recombinant Protein-containing	Protein-containing (PC) and chemically defined (CD)	2
	Complex formulation subgroups providing additional manufacturing challenge (CF)	
	Low melting point raw materials presenting milling challenge (MP)	
	Growth promotion test as measure of manufacturing success (GP)	

A total of 11 manufacturing lots using five media formulations representing specific process challenges (refer to Chart 1) were produced to assess the manufacturing process challenges as described above.

Chart 1. Validation Runs per Product Manufacturing Category



3. **Analytical Assessment:** Each lot was assessed for the following:

   a. Finished Product Specifications

   b. Growth promotion

   c. Product homogeneity (Refer to Table 2)

   d. Particle Size Analysis

Table 2. Acceptance Criteria for Process Validation

Homogeneity Testing Acceptance Criteria	
Amino Acids	< 10% RSD
Vitamins	< 10% RSD
Trace Metals	< 15% RSD
Finished Product Specification	Pass
Particle Size Analysis	For Information Only; To be reviewed for alignment with Lenexa d90 guidelines

Processes were controlled and validated based on critical process parameters identified during system impact assessments and defined during engineering studies. Where appropriate, these critical parameters for pre-blending, milling and post-blending were harmonized between Irvine and Lenexa. For example equivalent milling speed and product temperature specifications were applied. However, blending times were optimized based on equipment design at the Irvine facility.

Following post-blending of the batch, representative samples were taken throughout the packaging operation at specified intervals. A detailed sample plan was prepared in advance of PQ with a scientific rationale to justify sample and test requirements. Product homogeneity was evaluated by quantitative analysis of selected raw materials including amino acids, vitamins and trace metals. In addition, samples were tested against established finished product acceptance criteria, including growth promotion testing, where applicable. Pre-determined acceptance criteria was harmonized with those applied at Lenexa (Refer Table 2). Non-compendial test methods were validated prior to the PQ program and all internal test methods were harmonized with Lenexa.

In-process hold times were qualified to support routine production; this was built into the sample plan.

Case Study

Following the successful completion of the above Performance Qualification, a Case Study was conducted to demonstrate the practical comparability between the Lenexa, Kansas and Irvine, Scotland dry powder media manufacturing sites. The case study includes the following:

1. Assessment of Chemical Composition
   - Amino Acids
   - Vitamins
   - Trace Metals
2. Cell Culture Growth & Viability
3. Finished Product Specifications
4. Particle Size Analysis

Cleaning Validation

The cleaning validation strategy proposed for the DPM facility at Irvine is consistent with the approach used previously for cleaning validation at the Lenexa site.

Equipment cleaning processes were controlled and validated based on the critical parameters of Temperature, Action, Concentration and Time (TACT) and the associated Standard Operating Procedures.

Where appropriate, these critical cleaning parameters were harmonized between Irvine and Lenexa. For example equivalent cleaning agents and concentrations were used. However, temperature and time were optimized based on equipment design and engineering runs at Irvine.

A risk assessment was carried out by the Lenexa R&D team to identify representative products for the cleaning validation exercise. This assessment took into account the contamination risk to follow-on batches based on raw material solubility, concentration, production history at the Lenexa facility and ease of detection.

In conclusion a batch matrix which brackets batch volume and representative media in each production line was developed and used as a basis for validation (Refer Table 3). Validation of all automated and manual cleaning processes included triplicate runs to demonstrate consistent and repeatable cleaning across all batch sizes.

Table 3: Cleaning Validation Batch Matrix

	Lot Size	Media Category	Product	Cleaning Challenge
Line 1 CIP	Min	Complex Protein-containing	24365C	MP, SOL, REP, PC
	Mid	Complex Chemically-defined	Media 1	CF, MP, SOL, REP
	Max	Complex Chemically-defined	Media 2	CF, MP, REP, RM
Line 2 CIP	Min	Complex Chemically-defined	Media 1	CF, MP, SOL, REP
	Mid	Complex Chemically-defined	Media 1	CF, MP, SOL, REP
	Max	Complex Chemically-defined	Media 2	CF, MP, REP, RM
200L IBC Cleaning Validation	Min	Complex Chemically-defined	Media 1	CF, MP, SOL, REP
	Mid	Classical	R0274	RM, MP, REP
	Max	Classical	D3187	REP
1000L IBC Cleaning Validation	Min	Complex Chemically-defined	Media 2	CF, MP, REP, RM
	Mid	Complex Protein-containing	24365C	MP, SOL, REP, PC
	Max	Complex Chemically-defined	Media 1	CF, MP, SOL, REP
2100L IBC Cleaning Validation	Min	Classical	R0274	RM, MP, REP
	Mid	Complex Protein-containing	24365C	MP, SOL, REP, PC
	Max	Complex Chemically-defined	Media 2	CF, MP, REP, RM

Key:				
	CF	Cleaning of complex subgroups, e.g. oils	REP	Media representative of major classification
	MP	Low melting point RMs potential for residue adherence	PC	Protein content poses cleaning challenge
	SOL	Poor solubility RMs presenting cleaning challenge	RM	RM interaction potential poses cleaning challenge

Sample requirements and predetermined acceptance criteria for cleanliness were harmonized with those applied at Lenexa (Refer Table 4). All testing was carried out using validated test methods. Successful cleaning validation data based on this strategy, comprising passing test results and verified critical process parameters, were considered representative of all products transferred to the Irvine facility from Lenexa.

Table 4: Cleaning Validation Acceptance Criteria

Test	Purpose	Sample Location	Acceptance Criteria
TOC	To demonstrate removal of organic residues to acceptable levels	Final Rinse	TBD[2]
		Surface Swabs[1]	TBD[2]
Appearance	To demonstrate removal of visible product residues	Visible internal surfaces	Visually Clean
Conductivity	To demonstrate removal of cleaning agents and inorganic residues to acceptable levels	Final Rinse	<=3uS/cm
Bioburden	To demonstrate reduction to acceptable levels	Final Rinse	<=100 cfu/mL
Endotoxin	To demonstrate reduction to acceptable levels	Final Rinse	<=0.25 EU/mL

Clean and dirty hold times were defined and validated during this exercise to support routine production.

Critical Utilities

The following critical utilities were installed to support the new facility. These were specified, designed and qualified in accordance with the principles outlined in recognized industry guidance documents, for example the ISPE baseline guides. All critical utilities were subject to extended PQ testing over a one year period to verify performance and consistency during routine operation. Regular reviews were carried out during this qualification phase and approved routine test plans were implemented.

- Purified water, tested to EP and USP monographs
- Clean compressed air
- Clean nitrogen
- HVAC

Room Classifications and Environmental Conditions

All DPM manufacturing was carried out in areas designed to Grade D specification; elevated air changes have been implemented in rooms where open powder was exposed. The room classification strategy has been harmonized with the Lenexa facility and is deemed equivalent in all processing areas.

As a minimum the following parameters were continuously monitored via a validated facility monitoring system:

- Humidity in all areas where product is exposed
- Temperature in all areas where Raw Materials or Finished Products are stored
- Pressure differentials for all classified process areas and interlocks

The location of continuous monitoring probes were based on risk assessment and/or temperature mapping data acquired during PQ.

A failure mode and effect analysis were carried out to determine high risk areas for sampling throughout the DPM facility for viable testing. Based on this assessment, and current practice at Lenexa, an environmental monitoring program was implemented. This involves weekly monitoring of air and surface samples for viable organisms.

Ongoing Compliance

Validation status of the DPM facility was maintained through the effective implementation of standard operating procedures, maintenance and calibration programs, site change control, new product evaluation and transfer assessments, management review and a comprehensive routine validation schedule.

Routine validation requirements were defined based on the results of the Irvine PQ studies, corporate guidance and harmonization with the routine validation plans in place at the Lenexa facility.

Contingency Planning

This project was supported by the staff and experience of the Lenexa site. Both facilities have applied similar design principles and validation strategies, as detailed within this document. The products selected for PQ studies at Irvine have been included in successful qualification activities at the Lenexa facility. The use of equivalent products, and the application of the same acceptance criteria, clearly produce comparable data between the two facilities. This method of implementation ensures that harmonized and equivalent products were provided from both the Lenexa and Irvine facilities.

Raw material specifications, finished product specifications, certificates of analysis and test methods were harmonized between Lenexa and Irvine to ensure equivalency.

Further Information

We have designed and validated the Irvine Dry Powder Media facility to allow maximum flexibility and to meet our customer needs. If you have any questions or feedback on this white paper please contact your sales representative.

The Irvine DPM facility is available to audit on request.

Abbreviations

ACF Animal component free, ***CFR*** Code of Federal Regulations, ***CIP*** Clean In Place, ***COP*** Clean out of Place, ***CSD*** Cell Sciences Development, ***DPM*** Dry Powder Media, ***EP*** European Pharmacopoeia, ***FAT*** Factory Acceptance Testing, ***FDA*** Food and Drugs Administration, ***FMS*** Facility monitoring System, ***GAMP*** Good Automated Manufacturing Practice, ***cGMP*** current Good Manufacturing Practice, ***HVAC*** Heating, Ventilation, Air Conditioning, ***IBC*** Intermediate Bulk Container, ***IQ*** Installation Qualification, ***ISPE*** International Society for Pharmaceutical Engineering, ***MAC*** Maximum Allowable Carryover, ***MP*** Melting Point, ***OQ*** Operational Qualification, ***PQ*** Performance Qualification, ***PW*** Purified Water, ***RM*** Raw Materials, ***RSD*** Relative Standard Deviation, ***SAT*** Site Acceptance Testing, ***USP*** United States Pharmacopoeia, ***VMP*** Validation Master Plan

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