BioPhorum
FILL FINISH

The Rationale for Vial-Size Choices in the Pharmaceutical Development Process

Presentation for the NASEM Consensus Study Committee on the Implications of Discarded Weight-Based Drugs

Presenter: Kedar Gokhale, Associate Director *Janssen Research & Development* Biotherapeutics, Drug Product Development

on behalf of the BioPhorum Fill Finish Phorum

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What is BioPhorum?

Unique **global** collaboration

Powerful vehicle for **change**

Industry leaders and experts working in concert

Delivers results by pooling knowledge, practices and ideas

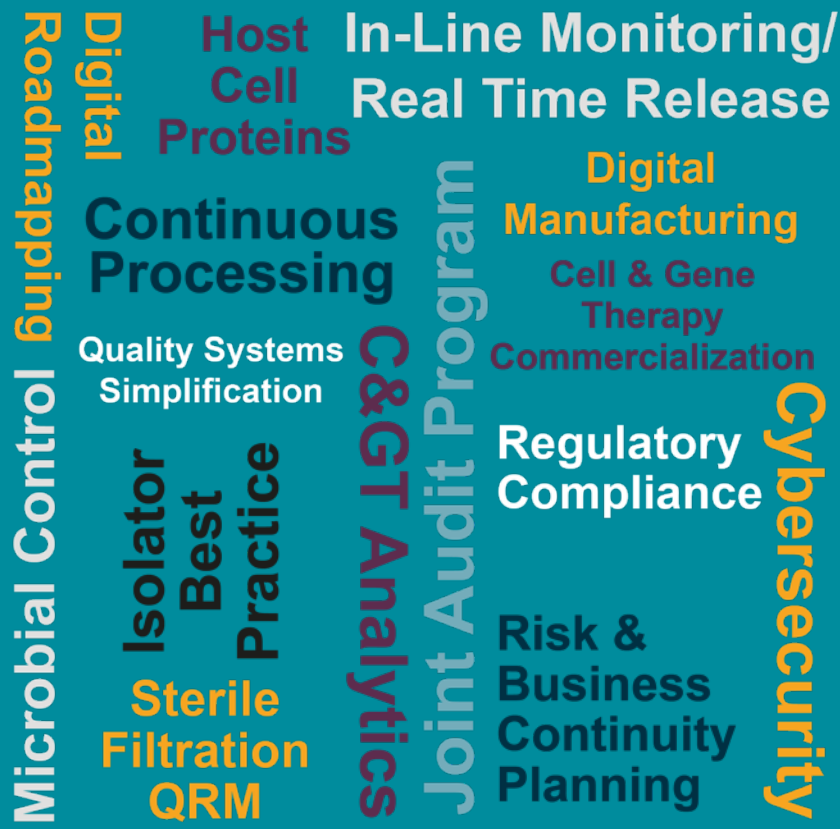
7 Phorums

>70 industry changing initiatives

90+ member companies

3400+ active participants

1 voice for the industry



BioPhorum FILL FINISH (FF)

In Fill Finish (FF) you will find representatives of the world's top sterile filling operations developing solutions to some of the most intractable technical and regulatory challenges. Members are now rolling out industry approaches to environmental monitoring and particle risk management; working together on rapid micro adoption and reconciling some of the critical challenges that Annex 1 brings to final filtration integrity testing and isolator disinfection.

The FF mission is to develop and implement best practice processes in drug product operations.

FF collaborates to develop and implement safe, predictable, lean and agile processes in drug product operations that biopharmaceutical pipelines need now and into the future and has strong representation of the top sterile filling operations in the world, both drug manufacturers and CMOs.

NASEM PROJECT TEAM

AstraZeneca

Ranjit Deshmukh, Senior Director, Global Network Lead Drug Product, Washington D.C.

Biogen

Jason Fernandez – Associate Director, Technical Development, Cambridge

Brian Thome - Principal Engineer, Parenteral Manufacturing Sciences, Baar

BioPhorum

Jannika Kremer, Facilitator, Stockholm

Dawood Dassu, Fill Finish Phorum Lead, Manchester UK

Bristol Myers Squibb

Ankur Kulshrestha - Associate Director, Parenteral Product Development, New Jersey

Yusuf Oni - Principal Engineer, Parenteral Product Development, New Jersey

Johnson & Johnson,

Kedar Gokhale, Associate Director *Janssen R&D* Biotherapeutics, Drug Product Development, Philadelphia

9 workstreams

10 face-to-face meetings

27 external publications and presentations

200+ active participants

25 member companies

How BioPhorum Hopes to Help the NASEM Consensus Study Committee

Value Proposition 1:

Inform and educate the committee on the rationale of vial size choices and implications of technical changes on the supply chain with the goal that the committee has the correct information and can ask questions/request further information.

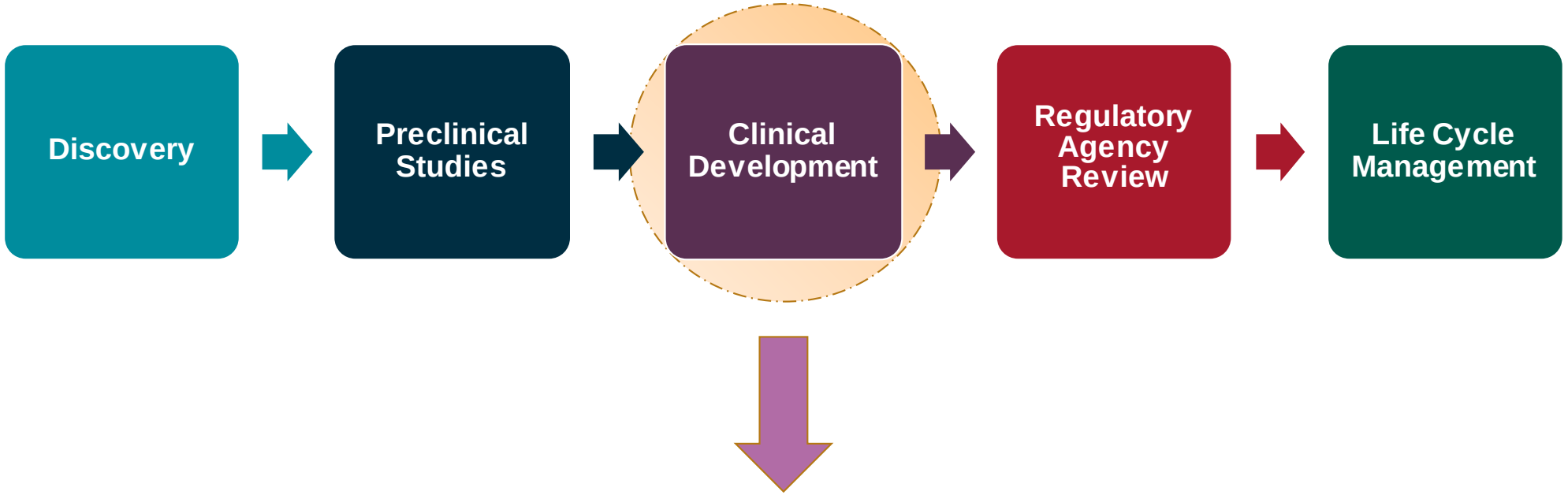
Value Proposition 2:

Understand the factors that may contribute to drug waste with an opportunity for biopharmaceutical companies to benchmark and showcase progress of viable technical solutions in the industry that help reduce the waste.

Value Proposition 3:

Align on and communicate what biopharmaceutical companies have identified as opportunities for policy makers to consider in order to collaborate in efforts to minimize drug wastage.

High Level Overview Pharmaceutical Development



- Clinical studies (efficacy and safety) inform the ultimate commercial dosage strength and dose volume.
- Iterative process requiring flexibility in dose strength / volume in early development stages.
- The target product profile is understood to evolve through clinical development. The drug product presentation is updated to reflect the clinical evolution of a molecule.

Fixed Dose Versus Weight Based Dosing

Clinical Perspective: Weight-based versus fixed dosing is based on several clinically determined factors, including efficacy and safety of the product. Products with broad efficacy and safety data (based on clinical trial data) are generally more amenable to fixed dosing.

Weight based	Fixed Dose

• Dose administered based on patient's weight
  • Dose volume adjusted per patient weight to facilitate administration of correct dose
  • Dosage form must support a range of potential doses, impacting utilization of contents
	• Dose/dose volume administered independent of patient's weight
	  • Provides flexibility to optimize single dosage form and minimize overfill volume within manufacturing capability
	  • *Most effective way to reduce drug product wastage*

Typical Factors Considered When Selecting Vial Fill Volume

Formulation

Manufacturing

Regulatory

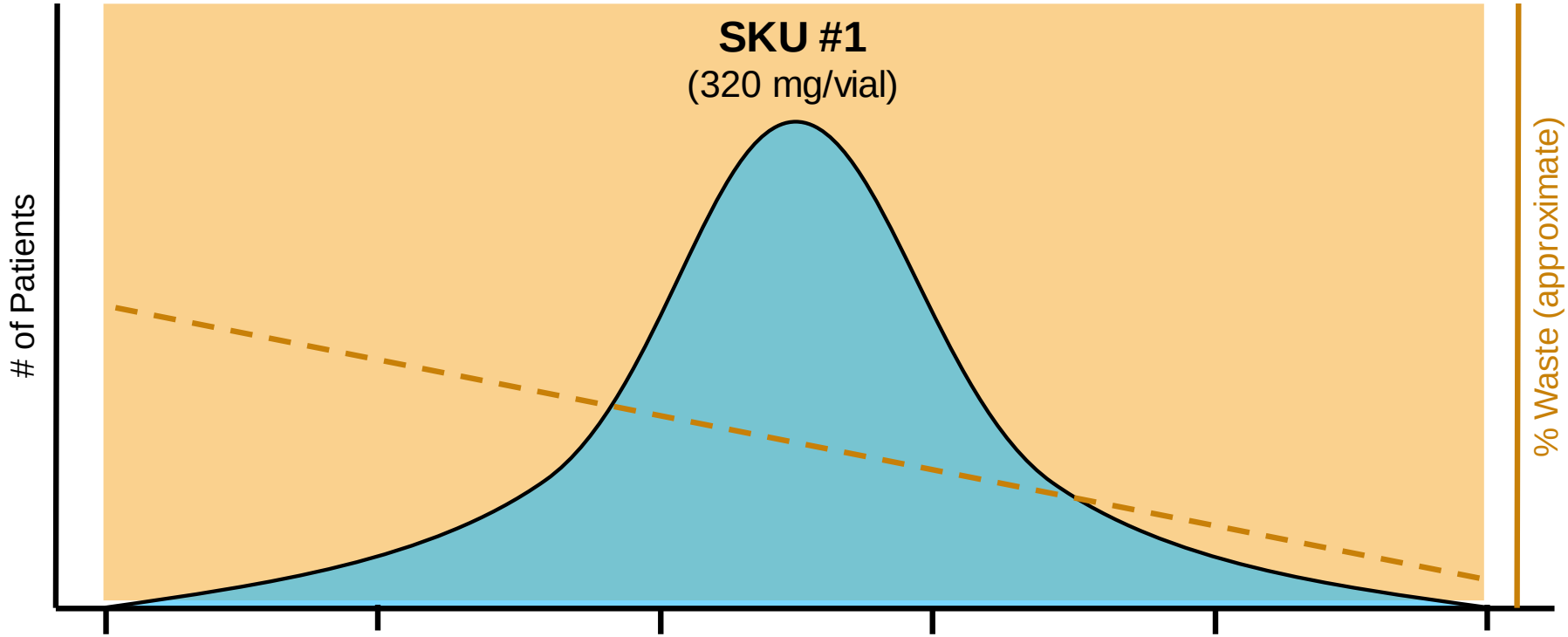
e.g. USP 1151 & 800 & FDA guidance on product design to minimize medication errors

User

e.g. user dexterity, ease of withdrawing volume, use of CSTD

Illustrative Example: 3 mg/kg Dose & 50 mg/mL Drug Product

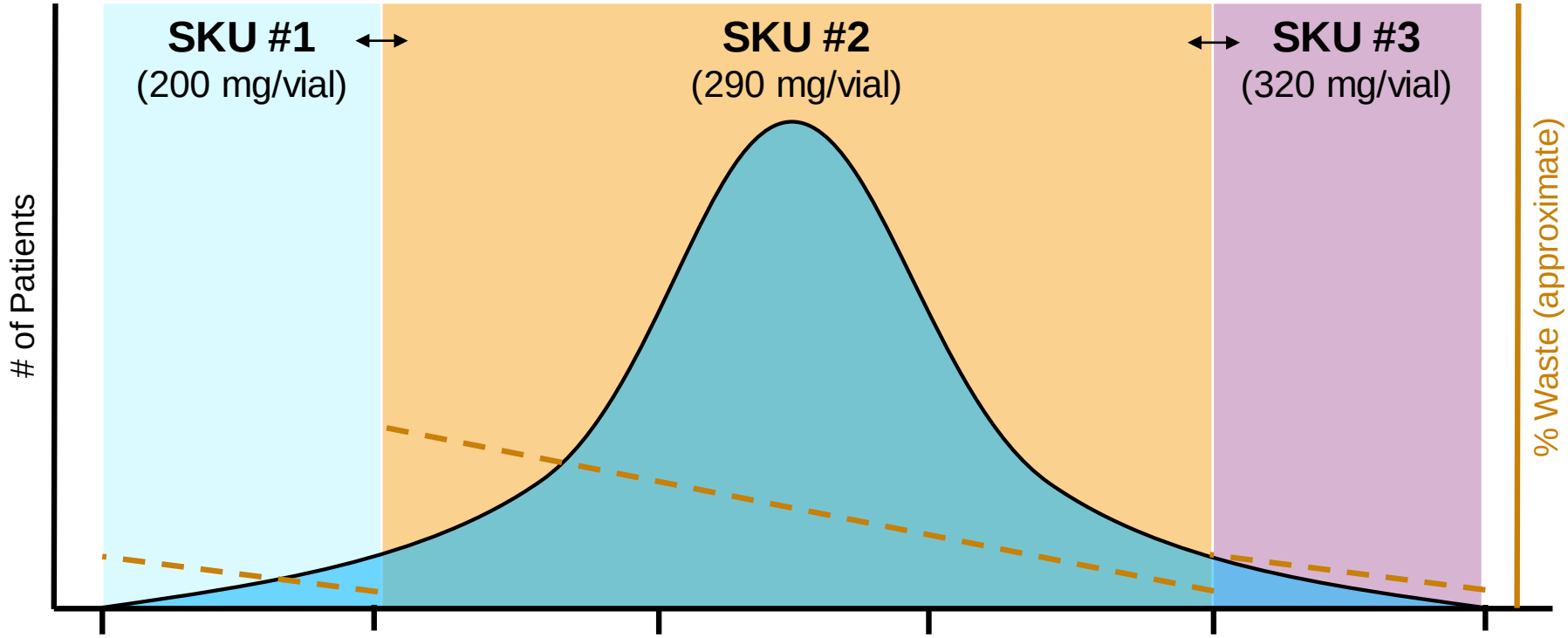
- A single drug product vial presentation (SKU) contains enough drug to cover dose range but results in high wastage when lower weight patients are dosed.
  - Weight range is highly variable, resulting in highly variable dose volume requirements



Patient Weight	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
Resulting Dose	150 mg	180 mg	210 mg	240 mg	270 mg	300 mg
Dose Volume	3.0 mL	3.6 mL	4.2 mL	4.8 mL	5.4 mL	6.0 mL

Illustrative Example: 3 mg/kg Dose & 50 mg/mL Drug Product

- Developing multiple SKUs may help reduce wastage in a vial.
  - However, all SKUs must be developed, validated and manufactured; representing a multiplier of effort (akin to developing multiple drug products).



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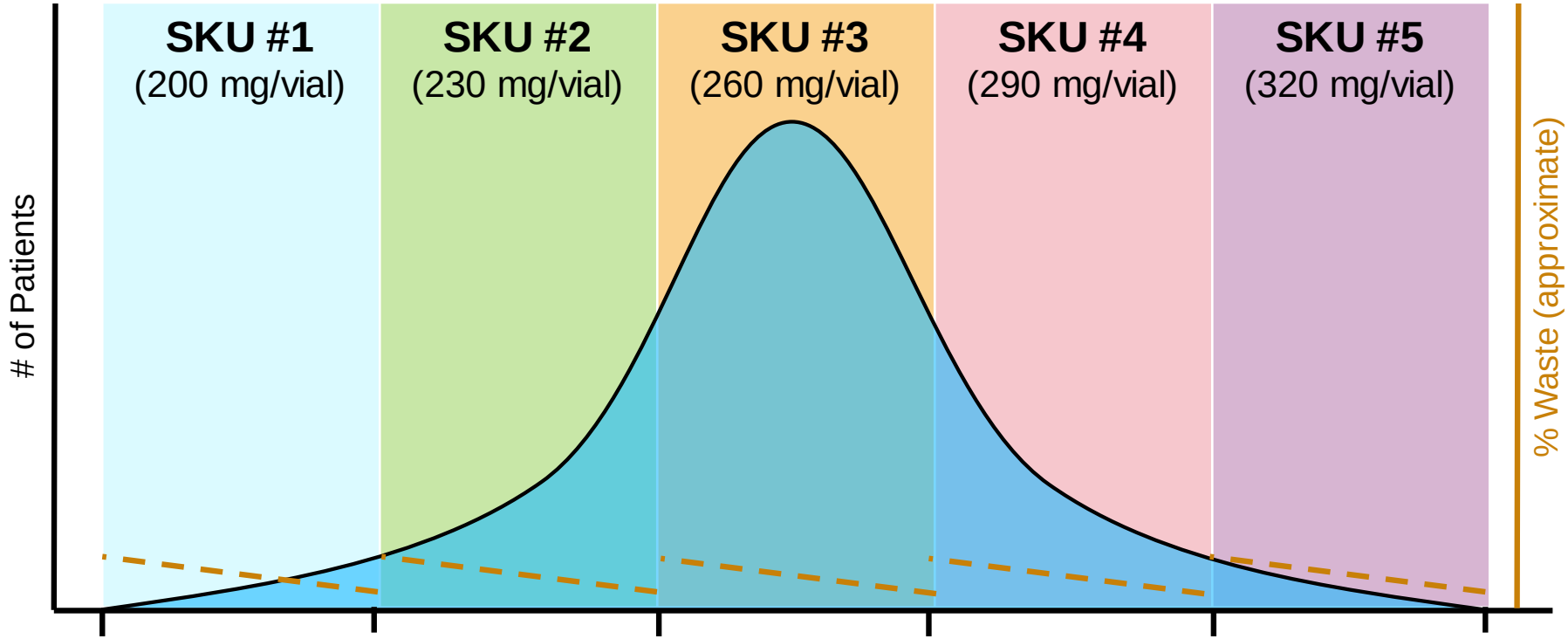
Illustrative Example: 3 mg/kg Dose & 50 mg/mL Drug Product

- Increasing SKUs narrows useful dose range, appearing to minimize wastage.
  - As all SKUs must be manufactured, maintained and inventoried, wastage is shifted upstream in supply chain. At a certain point, overall wastage is greater.



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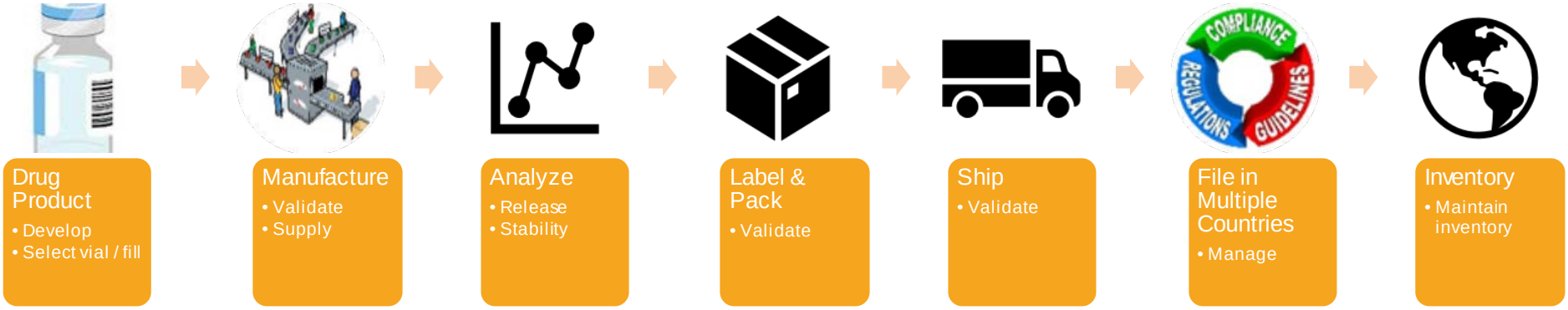
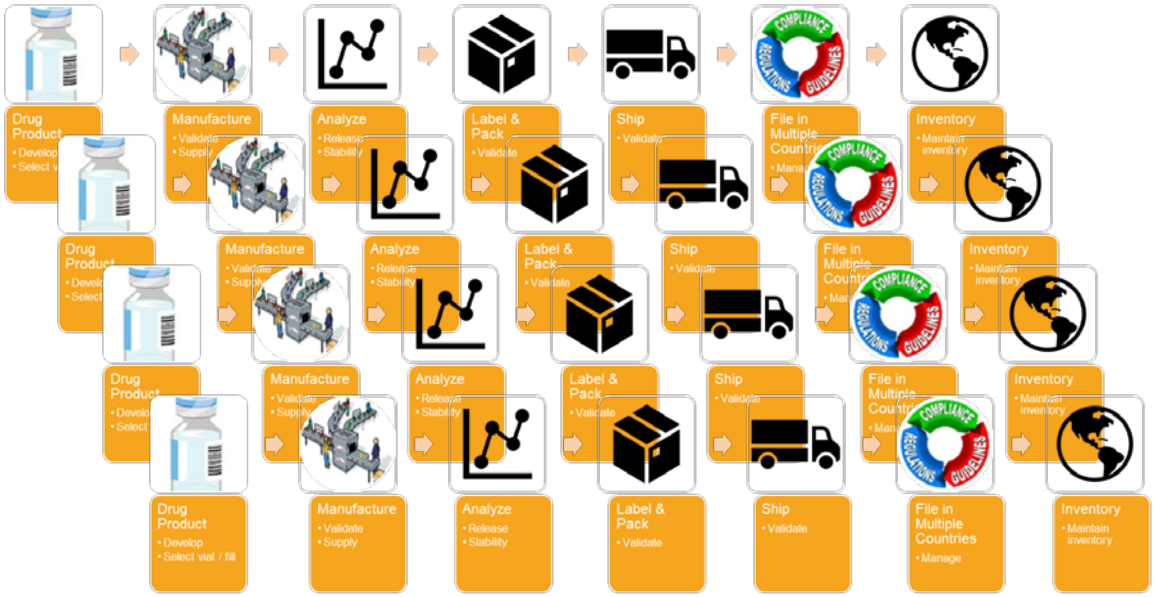
Multiplication of Effort, Inventory, and Wastage

For a Single SKU:



For Multiple SKUs:

Multiplication of effort leads to multiplication of wastage at each step.



What the Industry Is Already Doing to Reduce Drug Waste in the Supply Chain?

- SKU mapping of products to minimize wastage.
- Moving from vial-based product to prefilled syringe product when appropriate (i.e. subcutaneous dosage forms).
- Where appropriate proactively develop multiple SKUs, understanding not all will be marketed, to anticipate clinical outcomes / approved label.
- Optimize vial size for dose. Refine through life-cycle as necessary.
- Actively working to improve the shelf life of products – to reduce wastage in field.
- Move towards fixed dose where possible.

Collaboration Opportunities to Help Waste Minimization

- Broad, efficient and consistent access to a forum for proactive regulator engagement and dialogue on science-based strategy.
- Allowing more flexible bracketing approaches during development that can translate into a final dosage form would be useful.
- Global harmonization
  - Regulators can help simplify validation, manufacturing, and clinical pathway from weight based to fixed dose.
  - Minimize end user variability of administering drugs - for example, clearly defined guidance on CSTD (Closed System Transfer Devices) to make globally consistent practice.
- Acceptance of scientific rationale for establishing product specification and shelf life.
- Where applicable (i.e. subcutaneous, fixed dose), prefilled syringes can minimize overfill.
  - Enable efficient conversion for changing vial to syringe.
  - Risk-based combination product regulations for simple changes.

BioPhorum

Thank You

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Minutes and communication of F2F meetings v1.2

Minutes

The BioPhorum facilitator(s) will capture the key discussions, proposals and decisions in an **Event Report**. This report will act as the **Minutes** of the meeting and will

- detail the objectives, attendees and agenda
- include **hyperlinks** to all the materials shared in the event and an **executive summary**. All materials shared via hyperlinks will be in pdfs to lock down the contents in their presented form.
- Contain **photos** of the presenters and the team to help participants put names to faces after the event. If you do not want to be photographed please let the facilitator know.

Our aim is to **circulate** the Event Report in draft form within six working days of the meeting, to all the participants. A final draft will then be made available to all other workstream reps and Phorum Leaders (L2s).

Circulation to guests will be at the discretion of the facilitator(s) and team.

Photos of presentations must only be taken with the express agreement of their author.

Communication

Often discussions in meetings are exploratory and involve testing ideas, solutions and approaches.

We ask that all representatives in the meeting and dialling in respect the unformed state of discussions and agree not to comment on the discussions publicly on social media or report on the discussions on open public channels, during the meeting and until the final draft of the Event Report has been circulated and any messaging and communications strategy of the team has been agreed.

This is not a bar to representatives communicating about the meeting with peers, colleagues and stakeholders in their own organisation, this is very much encouraged.

Supplier interactions policy v3.0

The BioPhorum Operations Group (BioPhorum) facilitates a cross industry collaboration process for Biopharmaceutical developers and manufacturers with the aim of accelerating the rate at which the biopharma industry attains a mature and lean state benefitting patients and stakeholders alike. Collaboration modes include best practice sharing, benchmarking, joint-solution development to common challenges, definition of standards requirements and formation of collective perspectives to mutual opportunities and regulatory guidelines.

Biopharmaceutical developers and manufacturers recognize the legally enforceable duties they have including the responsibility to control the quality of materials from their suppliers. From time to time BioPhorum-facilitated collaboration requires, and benefits from, supplier interaction.

Suppliers are providers of supply chain materials such as chemicals, glass, components, excipients, and media. They are also providers of process equipment such as single use systems, engineering parts and consumables. BioPhorum-facilitated supplier interactions may involve: harmonizing manufacturer requirements and communicating these to suppliers; seeking feedback on proposed standards; gaining opinions and ideas related to business process improvement; use of problem solving tools; and gaining support for new ways of working.

The ultimate goal of the BioPhorum collaboration is to strengthen competition, assure product quality and protect patient supply.

The purpose of this document is to set out the principles and policies that BioPhorum follows to ensure that BioPhorum-facilitated supplier interactions are conducted in the correct and appropriate way to meet all legal and business compliance requirements.

Underlying Principles and Policies

Competition Laws: All supplier interactions will comply with anti trust and competition laws and have regard to BioPhorum's anti-trust compliance statement

Member responsibilities: Individual biopharma companies are responsible for defining their requirements of suppliers.

Innovation and commercial interests: All supplier interactions will recognise and respect the need for suppliers to innovate and pursue their own commercial interests.

Intellectual Property: All supplier interactions will respect suppliers' intellectual property rights.

Confidentiality / Non Disclosure: All supplier interactions will take into account, respect and encourage compliance with confidentiality and non-disclosure agreements.

Equal Treatment: All suppliers will be treated equally

Communication: These principles, policies and procedures will be communicated to BioPhorum members and suppliers whenever supplier interactions are planned or are taking place.

BioPhorum responsibilities

- It is the responsibility of BioPhorum Directors to ensure that these principles and policies are upheld and procedures are in place to support them.
- BioPhorum will educate and train its staff so they understand and follow these principles and policies and are able to communicate them when needed.
- BioPhorum documentation will reference or directly include relevant parts of the Supplier Interaction Policy.
- BioPhorum will establish and maintain records to demonstrate compliance with these principles and policies.

Code of Conduct – BioPhorum information sharing v3.0

Introduction

The BioPhorum Operations Group (BioPhorum) is a cross industry collaboration with the aim of sharing best practice in the area of Operational Excellence.

Participation in BioPhorum is restricted to authorized member company representatives as described in the Principles of Membership Agreement.

While sharing information is central to the process of this collaboration, it is important to understand what information is appropriate to share. Our companies have a great deal of confidential information and intellectual property that should not be shared within BioPhorum.

This document seeks to guide the reader so that the individuals and companies involved follow the correct code of conduct and problems are avoided.

It is the clear and stated intention of BioPhorum that the Group and its activities are conducted at all times in full compliance with relevant competition/anti-trust rules.

Responsibilities

It is the responsibility of every person who participates in a BioPhorum event or sharing activity to make sure they are aware of what information is appropriate to share. Furthermore, all participants are responsible for vetting any information to be shared via their company's public disclosure review processes and that all information shared is free of any "Confidential" stamps or markings.

The key contact (L2) for each member company should ensure confidentiality and that IP issues are highlighted to their colleagues and all applicable company policies regarding external collaboration and public disclosure are adhered to.

The BioPhorum facilitators are responsible for reminding all participants of their obligations with respect to information sharing.

Sharing information

The following list is representative of the types of disclosures commonly allowed by corporate policies. BioPhorum participants should review their company policies to ensure they are in compliance prior to any disclosures. Information in the following areas is typically allowed:

- Operational excellence best practice models
- Management approaches and philosophies
- Organizing and planning ways of working
- Non-product or process specific generic operating procedures
- Information in the public domain
- Information provided by suppliers which would ordinarily be shared with customers
- Non-product or process specific generic engineering or technical information relating to process equipment
- General learning and 'context' conclusions from QA and Regulatory activity

Sharing information from the following areas is typically prohibited by corporate policies

- Product related information
- Product related process data which constitutes intellectual property
- Specific audit or regulatory inspection findings or observations
- Product specific analytical methods
- Specific cost numbers where a market advantage may result or a supplier might be disadvantaged
- Information that is marked as confidential by the member company or a supplier
- Price information of any type
- Proprietary information including intellectual property and patented processes and equipment

BioPhorum event participants should direct all questions regarding information disclosure to their L2 BioPhorum representatives or corporate legal departments.