

*ISPE Drug Shortage Survey: Next Steps*

## Understanding Global Regulatory Filings Timelines: Upgrading Aseptic Processing Equipment or Facilities

### Introduction

The International Society for Pharmaceutical Engineering (ISPE), a global organization of pharmaceutical professionals and regulators involved in drug manufacturing, aims to address complex technical issues affecting drug manufacturing and quality.

ISPE formed a Drug Shortage Task Force in late 2012 to help stakeholders better understand the root causes of global drug shortages while defining strategies that could prevent or mitigate them. This Task Force, composed of members from a cross-section of the pharmaceutical industry, met with the U.S. Food and Drug Administration (FDA) in late 2012 and agreed to conduct an extensive survey regarding drug shortages by early 2013. During the survey's development, the Task Force requested and received input from members of several health authorities, including the FDA, European Medicines Agency (EMA) and Health Canada.

ISPE published initial findings in June 2013.<sup>1</sup> As expected, the ISPE survey did not identify a single technical or manufacturing root cause for drug shortages; rather, the data confirmed the multi-factorial nature of this global issue. Consequently, the Task Force designed a plan to learn more about key issues revealed by the survey and develop recommendations.<sup>2</sup> One was the formation of several working groups, including what we are defining as “The CMC working group.” Currently, this group is examining how the pharmaceutical industry and health authorities can promote more rapid continual improvements that address aseptic facility and equipment issues highlighted in the survey data (e.g., harmonization of global regulatory change management requirements).

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<sup>1</sup> Report on the ISPE Drug Shortages Survey (June 2013), <https://www.ispe.org/drug-shortages-initiative>.

<sup>2</sup> ISPE Report, at 13. The report describes several other areas for future initiatives related to drug shortages. These include product development and technology transfer issues highlighted in the survey as well as evaluation of facility layout or design factors that may contribute to non-sterile drug shortages.

## Purpose

This paper considers issues that may affect or potentially prevent aseptic equipment or facility upgrades, notably:

- Aseptic equipment or facility upgrades frequently require approval by many health authorities before manufacturers may supply the market with products.
- Because regulatory reviews by health authorities are not performed in parallel, manufacturers normally must maintain dual operations (i.e., old equipment/facility and new equipment/facility) until receiving all required approvals.
- The risks and technical complexities associated with dual operations, including the increased complexity of material management and supply chain modifications, may increase the chance for a drug shortage.

The working group developed a model based on member feedback to help stakeholders understand the lengthy timelines required to upgrade aseptic processing equipment and facilities. The model describes the timelines for both upgrades and global regulatory approval. This paper will describe the model and propose steps to reduce the time required to upgrade aseptic equipment or facilities.

## Model Timeline: Key

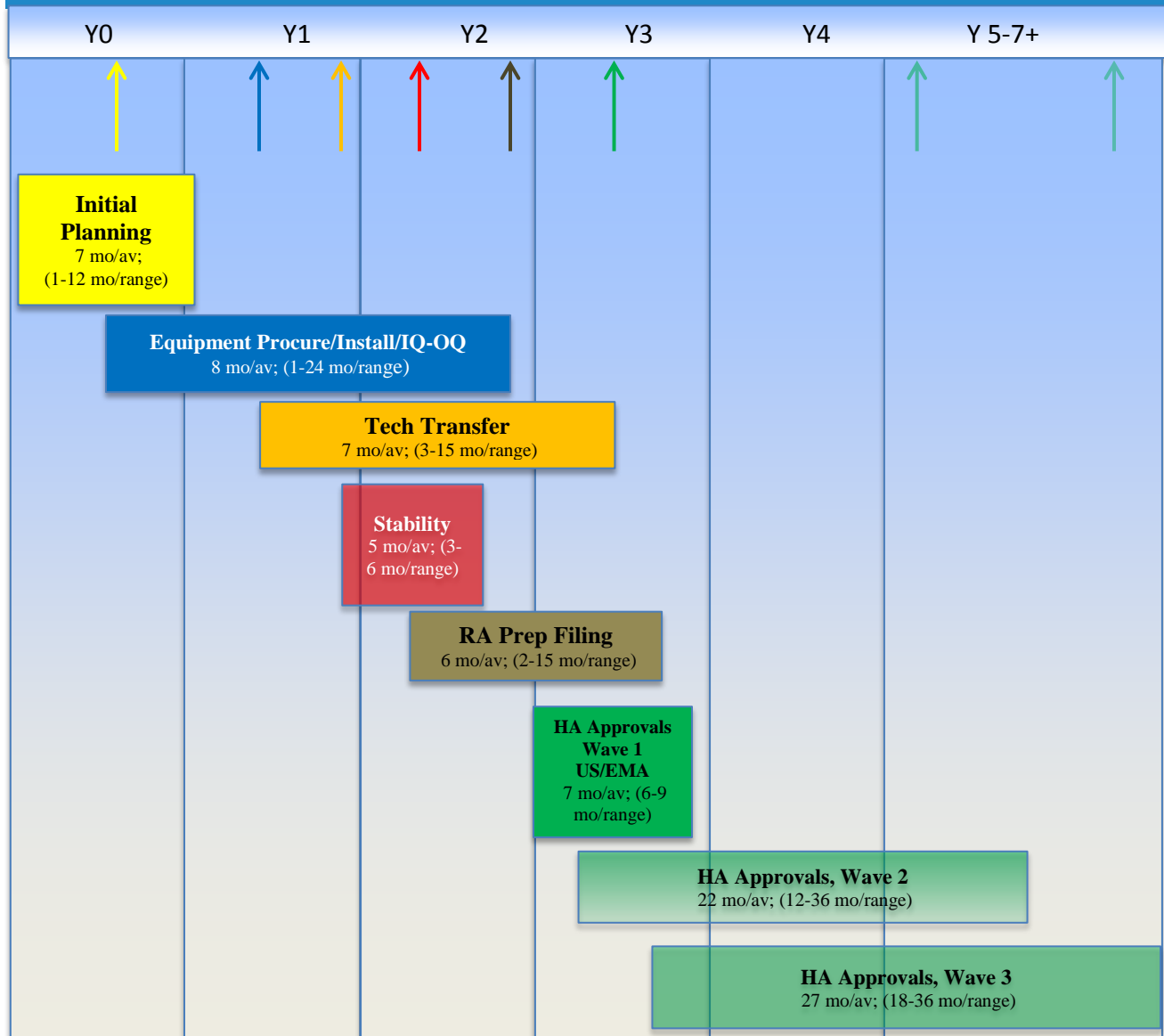
For uniformity, the Task Force created the following elements (box), appreciating the inherent overlap between some activities.

1. The “yellow” box describes initial planning activities (e.g., design and procurement) – 7 mo/av; (1-12 mo/range).
2. The “blue” box describes initial equipment activities for a new site (transfer to existing site) or an update of an existing site (e.g., equipment procurement, installation and qualification) - 8 mo/av; (1-24 mo/range).
3. The “orange” box describes general tech transfer activities - 7 mo/av; (3-15 mo/range).
4. The “red” box describes activities regarding biowaiver health authority (HA) alignment, if applicable (e.g., three month stability in parallel) - 5 mo/av; (3-6 mo/range).
5. The “brown” box describes the activities associated with preparing the HA filing for the particular CMC change (e.g., new equipment) - 6 mo/av; (2-15 mo/range).
6. The “green” box describe HA approvals in three distinct waves: Wave 1 includes the FDA and the European Union, where reviewers often are more receptive to discussions on risk-based approaches - 7 mo/av; 6-9 mo/range); Wave 2 (lag 22 mo/av; (12-36 mo/range) and Wave 3 (lag 27 mo/av; (18-36 mo/range) involve markets with longer approval timeframes and where HA's often are less receptive to discussions on risk-based approach, and follow strict approval processes.



## Model Timeline for Tech Transfer/Facility-Equipment Upgrade & Health Authority Review

*(Injectable aseptically filled drug product)*



- Notes:
- (1) Arrows represent average time for each element
  - (2) Timeline provided by ISPE members for large and small molecule products
  - (3) Timeline does not include BE studies; timeline based on post-approval changes only
  - (4) Timeline does not consider constructing new facility (out of scope)

## **Key Model Findings**

1. Based on the wide range of data, manufacturers may be able to reduce the timelines for several elements (i.e., initial planning, equipment (IQ/OQ), validation and tech-transfer).
2. Tech-Transfer is relatively short compared to the times for health authority (HA) approvals in all countries.
3. Facility upgrade is relatively short compared to times for HA approval in all countries.
4. It takes approximately seven years from the initial planning phase for an aseptic equipment or facility upgrade to secure approval from all global HAs.

## **Discussion**

Because HA reviews are not performed in parallel, manufacturers normally must maintain dual operations (i.e., old equipment/facility and new equipment/facility) until receiving all required HA approvals.

The risks and technical complexities associated with these dual operations, including the increased complexity of material management and related supply chain modifications, may increase the chance for a drug shortage and may help explain why certain manufacturers are reluctant to upgrade their aseptic equipment or facilities.

## **Next Steps**

1. To further develop its best practices to avoid or mitigate drug shortages associated with aseptic equipment or facility upgrades, ISPE will continue to leverage the subject matter expertise in its Communities of Practice (COP), Regulatory Compliance Committee and the Product Quality Lifecycle Initiative (PQLI) to enhance its technical documents and training (e.g., to optimize IQ/OQ/validation/tech transfer). This will include updates to ISPE's Technology Transfer Good Practice Guide.
2. ISPE will continue to collaborate with global HAs to harmonize the approval process for CMC changes. ISPE strongly supports a more science and risk-based post-approval change process.