Production Scheduling of Small Molecule API Manufacturing using SchedulePro Cloud®

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Simulation, Design, and Scheduling Tools for the Process Manufacturing Industries

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1 Introduction

This example describes how SchedulePro Cloud can be used to schedule production of a pharmaceutical product which is generated through a multi-step organic synthesis. These types of products are sometimes referred to as "small molecules", as opposed to "large molecule" proteins produced from biological processes. Organic synthesis of a molecule involves a series of chemical transformations which "build" that molecule from various raw materials and intermediates. This is a common practice within the traditional synthetic organic pharmaceutical industry. The number of steps ranges from very few (e.g., aspirin synthesis, which can be performed with a single reaction) to very many (e.g., oligonucleotide synthesis, which may require dozens or even hundreds of reactions). This example is equally applicable to production planning for multi-step syntheses of other types of (non-pharmaceutical) molecules in industries such as fine chemicals.

The synthesis route for this example is defined by the following set of sequential reactions. Note that these steps have been simplified to only include the key input molecules and product of a given step; inexpensive raw materials and byproducts are ignored. Therefore the reactions in these SchedulePro Cloud files are not necessarily "balanced" from a mass standpoint.

Step 1: RM-1 + RM-2 → Int-1

Step 2: Int-1 + RM-3 → Int-2

Step 3: Int-2 → Int-3

Step 4: Int-3 → API

The SchedulePro Cloud features covered by this document include:

- Defining Production templates (BOMs) and using them for the production of intermediate and final products.
- Determination of campaign sizes for different intermediates.
- Use of storage units to track and visualize intermediate inventories.

This example includes the following cases:

Case A – Base Case with Single Large Campaigns of Each Step

This case describes the four-step process and provides information on how certain parts of the project were defined. This case's production plan represents the production of 5,000 kg/yr of the final product

within a single processing suite. The production plan is fulfilled using four campaigns – all batches of the first intermediate are run first, all batches of the second intermediate are run next, etc.

Case B – Multiple small campaigns of each step

In this case, the original long campaigns of each recipe are broken into multiple mini-campaigns which are staggered over the course of the production plan.

Case C – Single large campaigns, but two production lines

Like Case A, Case C utilizes single large campaigns of each step. However, the steps are split between two production lines and therefore batches of multiple steps may be run in parallel.

Case E – Tracking labor demand

This is similar to Case C, except that operator labor has been assigned to various operations. This allows the simultaneous demand for labor to be visualized.

Each of the cases above is described in greater detail in the following sections. Note that this document does not attempt to explain all the details related to the creation of these models. For information on the basic steps required for creating models in SchedulePro Cloud, please refer to the user manual.

In order to load the complete examples into the application, go to the landing page, select the “Create Sample Workspace” option and navigate to the “Examples” tab. Select the desired example and click “Next”. On the final window, you may optionally edit the suggested name and then click “Create” to create the sample workspace.

The application creates the example workspace, which includes one scheduling board for each example case, and automatically switches to the first scheduling board. In order to navigate between the various example cases/scheduling boards, click the ⇄ icon in the information box at the middle-top of the page (see figure below) and select the desired scheduling board from the dropdown menu.

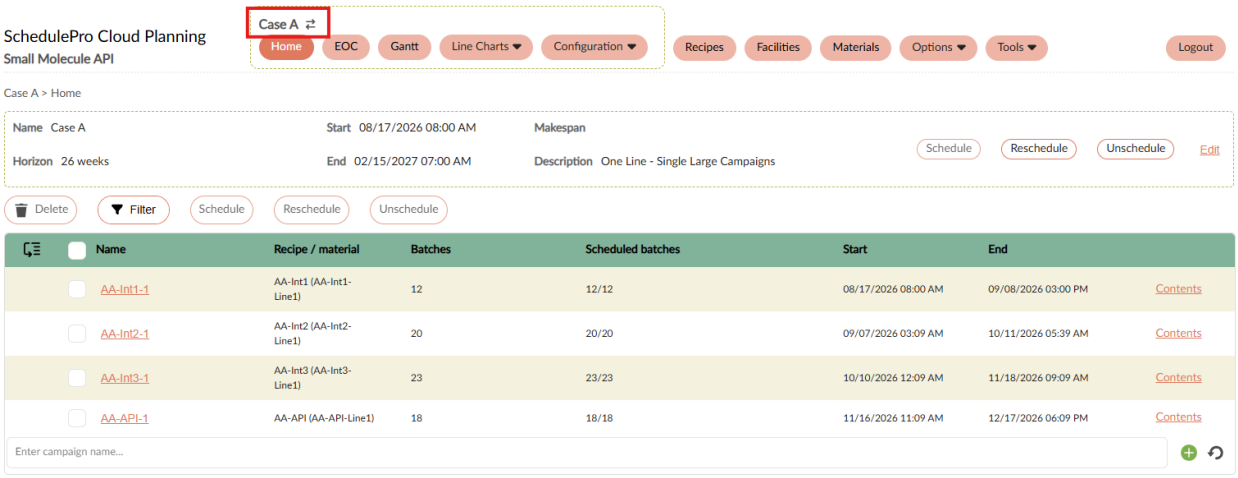


Figure 1: Switching scheduling board in a workspace

2 Case A – Base Case with Single Large Campaigns of Each Step

In this example, materials were created under the Materials node in the workspace. For instance, RM1, RM2, and RM3 were created as bulk pure components, so that the key raw material requirements could be accounted for later, when scheduling the campaigns. The properties dialog for one of these materials is displayed below. AA-Int1, AA-Int2, AA-Int3 and AA-API were created as bulk pure components, as well, which correspond to the intermediate and the final product.

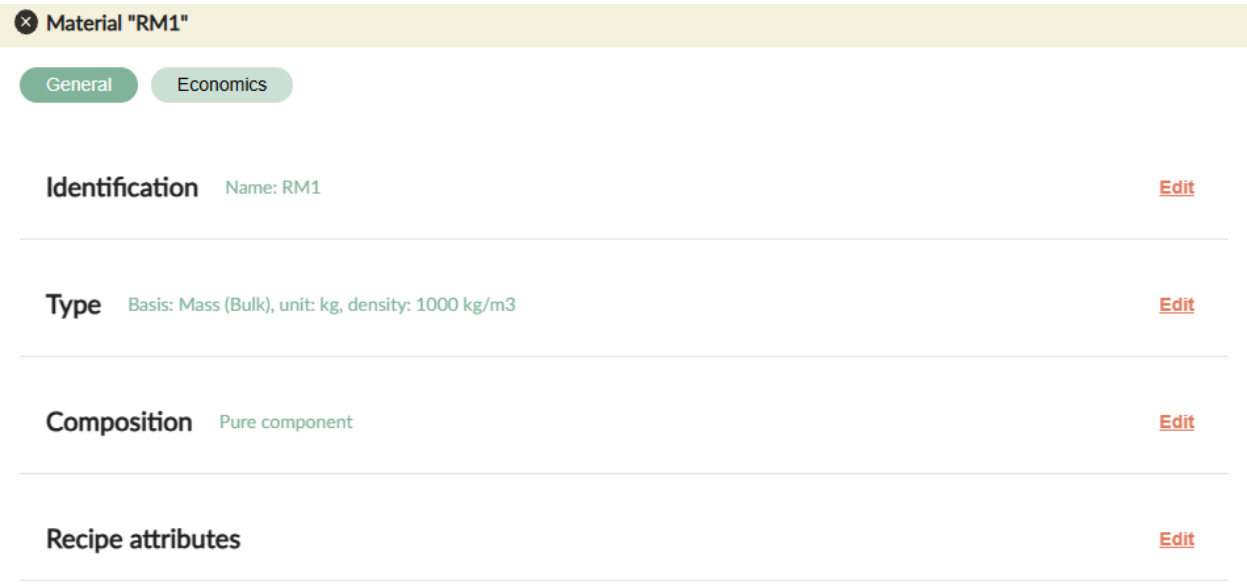


Figure 2: The Properties of Material "RM1"

Moreover, a PA Facility of two lines is available (Line 1 and 2). Units of each line are presented in the

Table 1: Unit equipment of the two production lines

Type of equipment	**Line 1**	**Line 2**
Chromatography column	C-101	C-201
Dryer	DR-101	DR-201
Nutsche filter	FL-101	FL-201
Reactor	R-101	R-201
Reactor	R-102	R-202
Blending tank	T-101	T-201
Blending tank	T-102	T-202

In addition, five Storage Units were created, under the Storage Units node of the **PA Facility-Line1&2**. A unit was assigned to each of the materials: RM1, AA-Int1, AA-Int2, AA-Int3 and AA-API. A capacity of 8,000 kg was specified.

In the figure below, **AA-Int1 Storage** was assigned to the material **AA-Int1**. Storage units will be discussed in more detail later in this document.



Figure 3: Creating a new Storage unit

Case A contains separate recipes for each step of the 4-step process, which are utilizing the Line 1 of the PA Facility:

- AA-Step1-Line1
- AA-Step2-Line1
- AA-Step3-Line1
- AA-Step4-Line1.

A portion of the recipe for the first step is shown below, by selecting the **AA-Step1-Line1 Contents** link, under the Recipes node of the workspace.

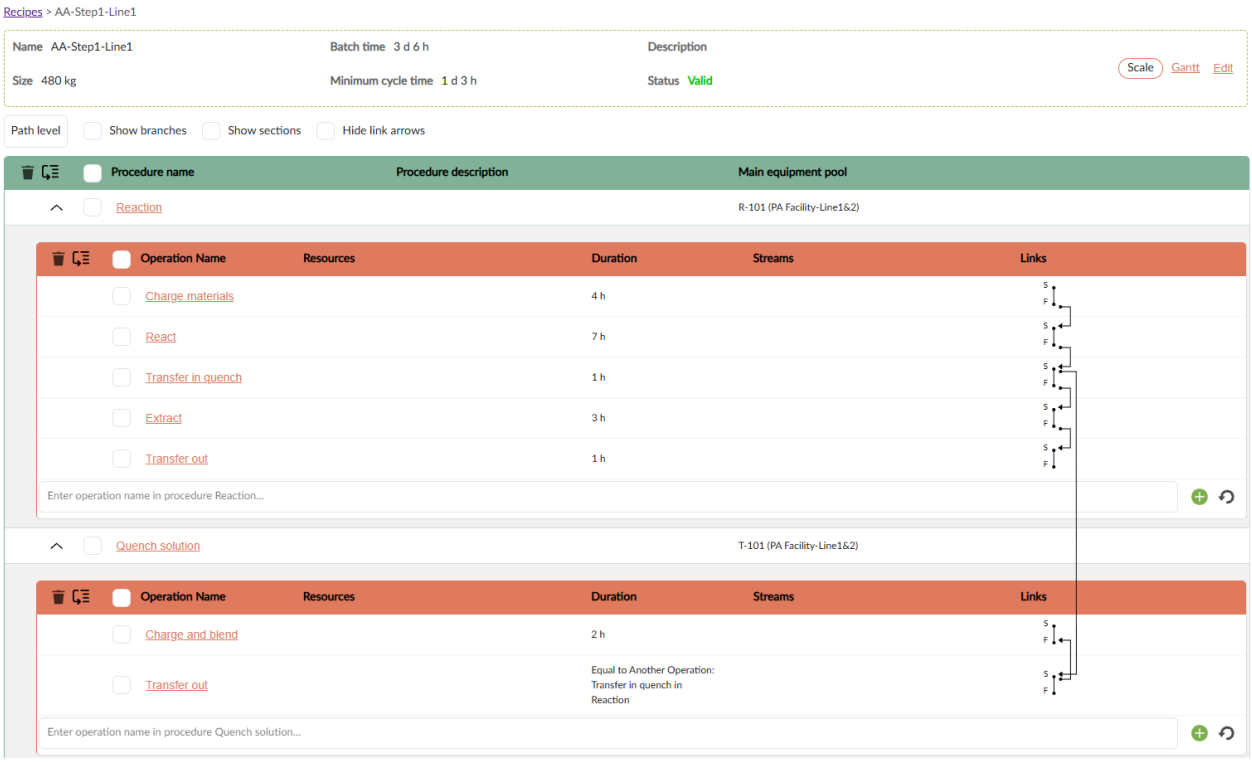


Figure 4: Part of the Recipe for Step 1 utilizing Line 1

This recipe is split into 11 unit procedures (Reaction, Quench solution, Product phase storage, etc.), each of which has multiple operations within it. The timing links between operations and procedures are displayed as black arrows (i.e., once the Charge materials operation in the first procedure is completed, the React operation begins, etc.). The main equipment units (R-101, T-101, etc.) assigned to each procedure are also shown. These assignments were made on the **Main equipment pool** tab of each procedure's properties dialog. The creation of recipes and assignment of their associated resources is explained in detail in the SchedulePro Cloud manual, the Tutorias and some of the SchedulePro Cloud examples. That information will not be repeated here.

A more-detailed view of the scheduling specifications for a given recipe can be obtained by selecting the recipe Gantt Chart link on the Recipes list. A portion of the Gantt chart for the AA-Step1-Line1 recipe is shown below.

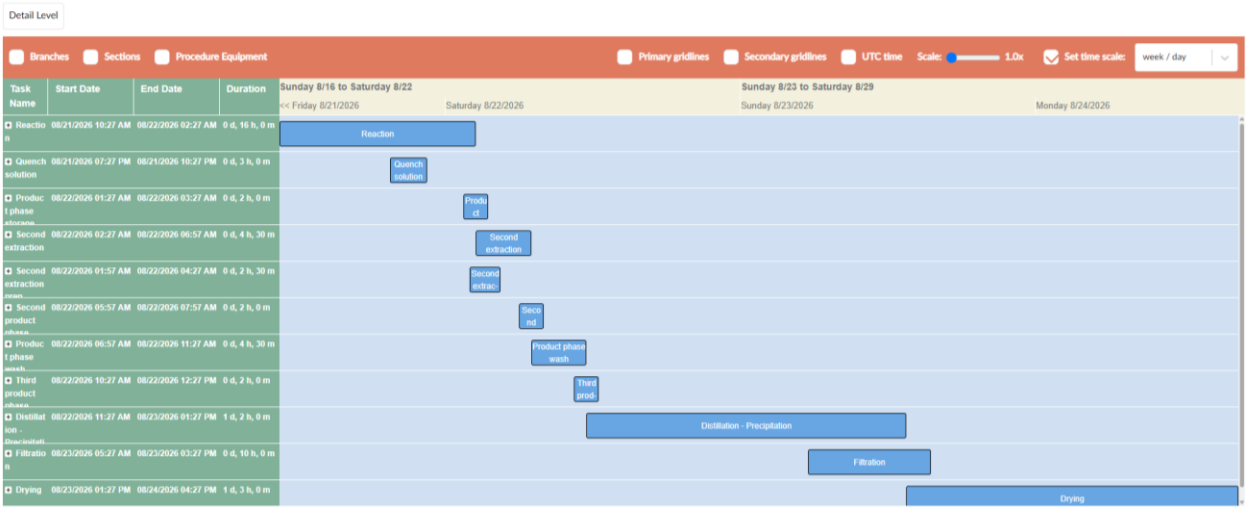


Figure 5: Part of the Gantt Chart for Step 1

This chart displays the durations as well as the start and end times (relative to the batch start) for each operation and each procedure. It provides an excellent way to check the recipe to ensure that the durations and timing links between operations have been specified correctly.

For each intermediate and the final product, a **Production template** was specified in the **Materials** node. The Production template contains information such as the recipe used to produce the product, the **Bill of Materials (BOM)** required for its production and the scaling factor used to adjust the quantities of all materials in the BOM to achieve the required production quantity.

For this example,

- for step 1, 248 kg of RM1 and 254 kg of RM2 are required to produce 480 kg of AA-Int1,
- for step 2, 280 kg of RM3 and 144 kg of AA-Int1 are required to produce 360 kg of AA-Int2,
- for step 3, 312 kg of AA-Int2 are required to produce 276 kg of AA-Int3 and
- for step 4, 346 kg of AA-Int3 are required to produce 284 kg of AA-API.

In the figure below, specifications for the production template of product AA-Int1 are shown. The recipe **AA-Int1-Line1** is selected for case with BOM amount factor equal to 1, in order to achieve the required batch size (480 kg). Corresponding adaptive inputs and outputs were declared. RM1 and intermediate products are drawn from their corresponding storage units, while the produced products are deposited into the appropriate storage units.

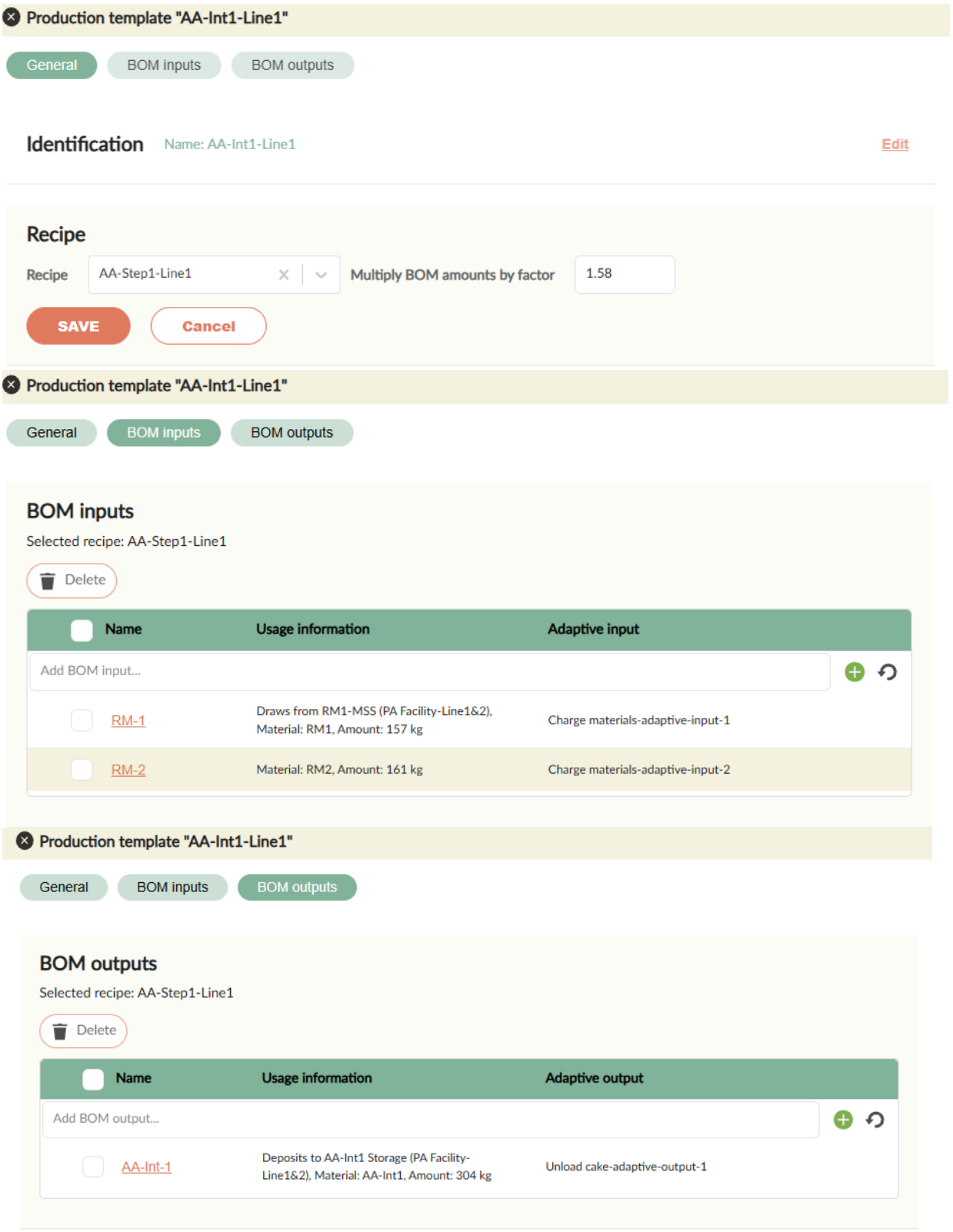


Figure 6: The production template specifications for AA-Int1

Once the production template is specified, the synthesis tree for AA-Int1 becomes available, displaying the quantities of raw materials required to produce one batch of this intermediate product.

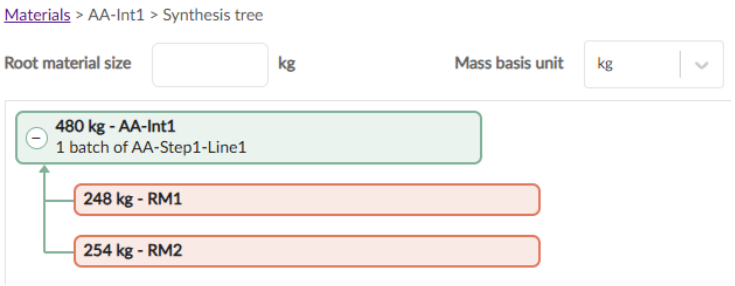


Figure 7: Synthesis tree of the AA-Int1

Keep in mind that the values listed in the BOM chart for a given material just represent the ***ratio*** *between the reagents and the product*; *they do not necessarily correspond to the batch size for each intermediate*. The actual amount of material that will be produced per batch of a campaign is determined by the recipe batch size and the amount factor within the production template (or based upon a modification to that batch size that may be specified during the creation of a campaign).

Also, keep in mind that these steps have been simplified to ignore inexpensive raw materials and byproducts. In addition, there are intermediate/product losses that take place due to incomplete reactions, as well as lost yield during purifications. Therefore the reactions in these case files are not necessarily "balanced" from a mass standpoint; the expressions below simply represent the ratios of the key inputs and outputs of each step.

Although a single 284 kg batch of AA-API is produced from 346 kg of AA-Int3, a single batch of AA-Int3 only produces 276 kg of this intermediate. Therefore roughly 1.25 batches of AA-Int-3 material are required in order to produce each full batch of AA-API. In other words, different numbers of batches will need to be performed for each step of the process. The synthesis tree of the final product displays these calculations, including the number of batches required at each process step and the quantities of raw materials and intermediates needed to produce one batch of the final product.

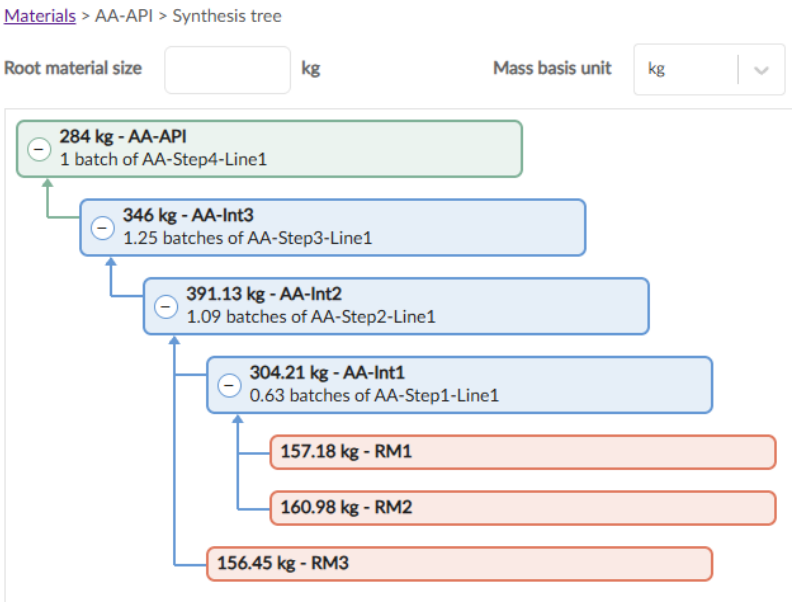


Figure 8: Synthesis tree of the AA-API

For example, if there is a 5,000 kg/yr market demand for AA-API, the number of batches of each recipe step are shown in the table below:

Table 2: Batch sizes and number of batches based on the products demand

Step #	Demand/Yr (kg)	Batch Size (kg)	# of Batches/Yr
1	≥ 5495	480	12 (12 x 480 = 5760 kg of AA-Int1)
2	≥ 7065	360	20 (20 x 360 = 7200 kg of AA-Int2)
3	≥ 6250	276	23 (23 x 276 = 6348 kg of AA-Int3)
4	≥ 5,000	284	18 (18 x 284 = 5112 kg of AA-API)

The Demand/Yr for Step 3 in the table above was calculated based on the 1.25:1 ratio between the mass of AA-Int3 consumed and the mass of AA-API produced in Step 4 (i.e., 346 kg of AA-Int3 consumed per 284 kg of AA-API produced). Since at least 5,000 kg of AA-API must be produced (using the Step 4 recipe), at least 6,250 kg of the Step 3 intermediate must be produced. The Demand/Yr for Steps 1 and 2 are calculated in the same way.

The number of batches for each step in the table above is determined based on the Demand/Yr of a given step and the Batch Size of that step (i.e., 18 batches of Step 4 are required in order to ensure at

least 5,000 kg of AA-API are produced.) Once the number of batches of each step have been calculated, they may be scheduled.

One way to fulfill the 5,000 kg AA-API production sequence summarized in the table above is to create single campaigns of each step, each of which runs on the same production line. This scenario was modeled in Case A.

After the production templates were completed, the 5,000 kg production plan of AA-API (including its intermediate steps) was ready to be scheduled.

The campaigns for each step were created in the **Enter campaign name..** input field of the **Home** page. Each campaign is material based and the appropriate production template is selected. Based on the values calculated in the **# of Batches/Yr** column of the table that was displayed earlier, the following campaigns were created.

- AA-Int1-1 campaign of 12 batches
- AA-Int2-1 campaign of 20 batches
- AA-Int3-1 campaign of 23 batches
- AA-API-1 campaign of 18 batches

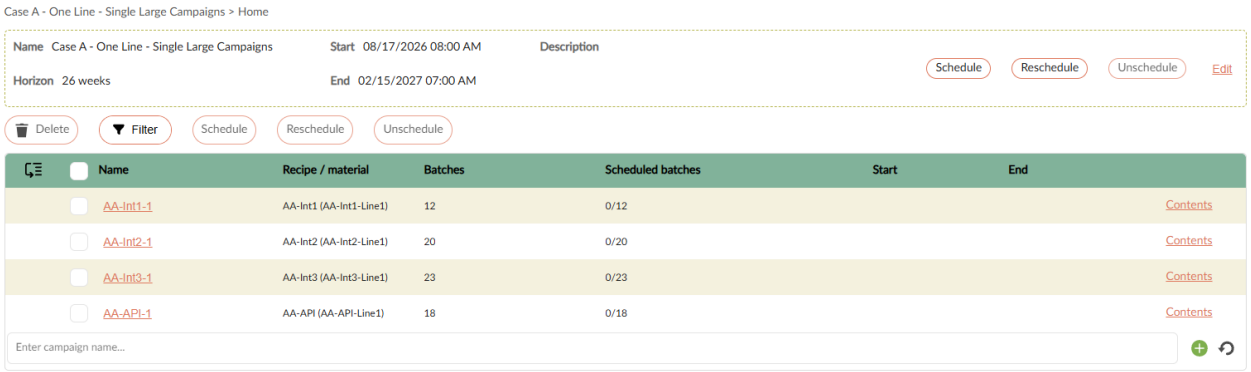


Figure 9: Scheduling board for Case A

A 3-day changeover time was also scheduled to occur at the end of each of the three first campaigns, to account for extended equipment cleaning and other changeover activities. That information was specified by clicking on the campaign, checking on the **Post (equipment) changeover** and clicking edit. In the side panel, changeover duration and scheduling options can be specified in the corresponding tabs (see figures below).

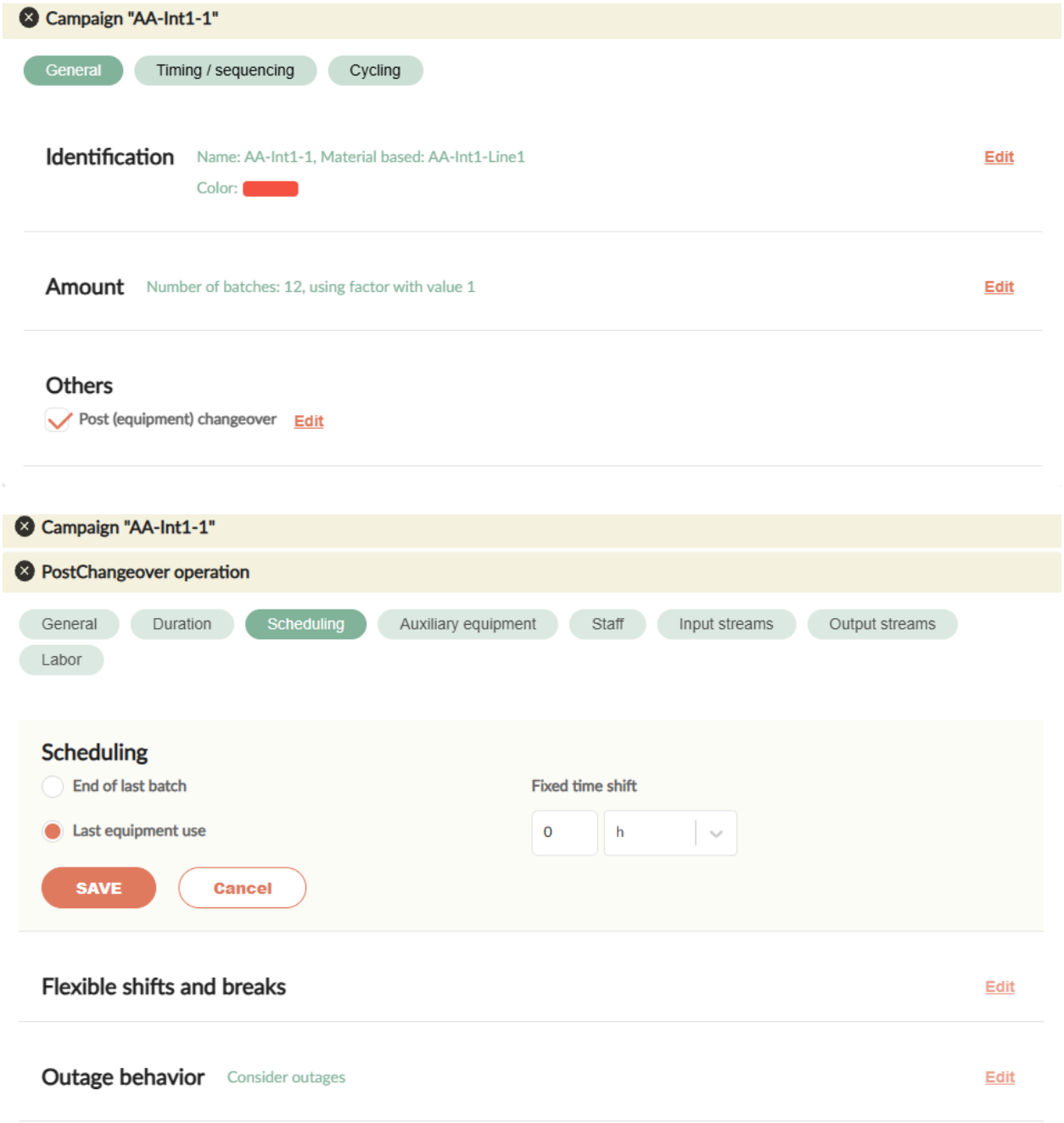


Figure 10: Setting the End-of-Campaign Changeover Duration and scheduling

After a single campaign was created for each step of the process (based on the required amount of each intermediate that was calculated earlier), all the campaigns were scheduled. The resulting EOC is shown below. This production plan has a makespan of roughly 18 weeks.

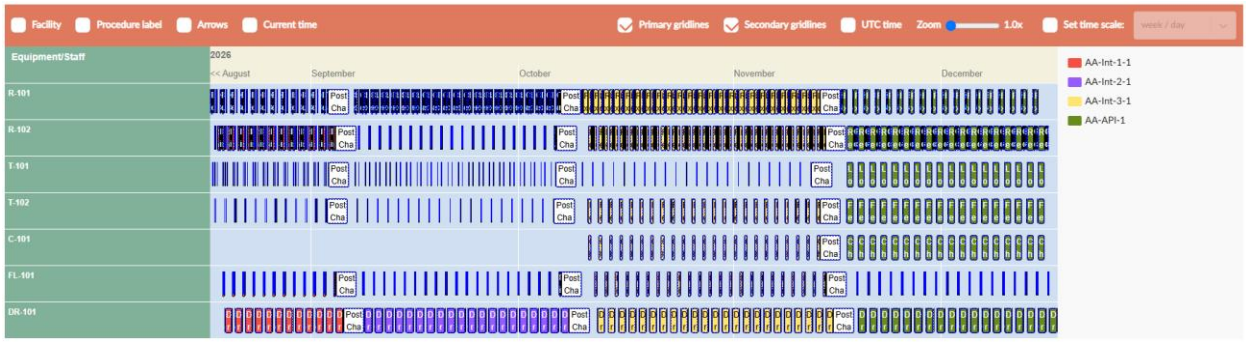


Figure 11: EOC for Case A: One Production Line; Single Large Campaigns for Each Step

While this production plan has the advantage of efficient utilization of the plant equipment, no AA-API product is ready for delivery to customers until the first Step 4 batches are completed during Week 14. This may be unacceptable if customers need the product sooner. Another issue with the Case A production plan is that large amounts of intermediate inventory must be stored in the warehouse. This can be seen in the EOC below, which shows that over 5,000 kg of inventory storage must be available for each intermediate at various points in time. The Inventory Chart is shown below for each of the intermediate products. To open the inventory chart, click on the Line charts, select Inventory chart and select from the drop down menus the Storage Unit, the Amount unit and the Rate unit. Click on Refresh chart button at the right part of the workspace.

This process was followed for all three intermediate inventory charts.

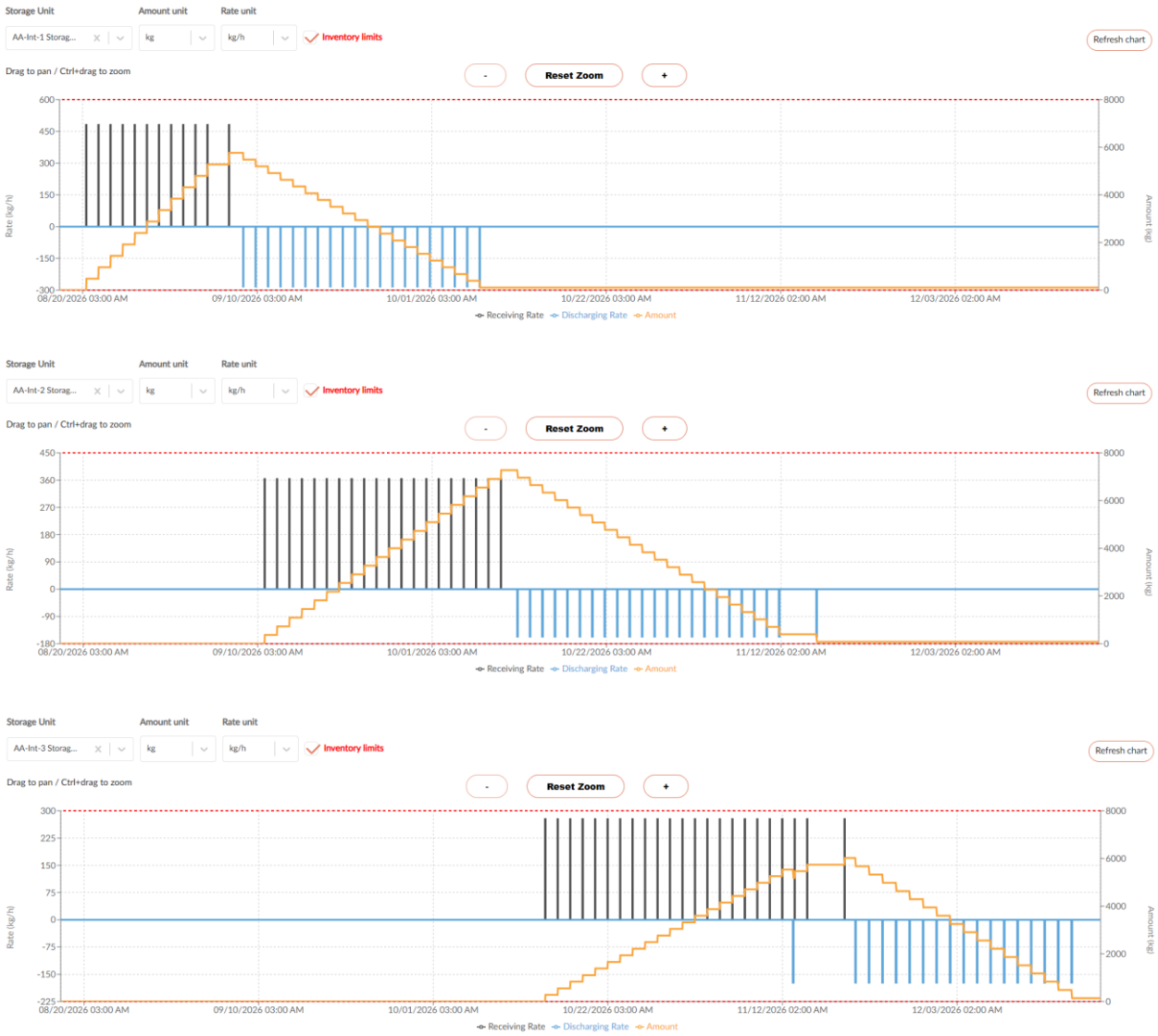


Figure 12: Inventory Charts for the intermedia products in Case A

3 Case B – Multiple Small Campaigns of Each Step

In contrast to Case A, Case B splits each of the original campaigns into multiple smaller campaigns of 3 to 6 batches each. As before, there is a 3-day changeover between campaigns.

This results in a significantly less-efficient schedule due to the higher number of time-consuming changeovers between these short campaigns. As a result, the makespan for the production plan increases to 22 weeks (from 18 weeks previously). The EOC for this scenario is shown below.

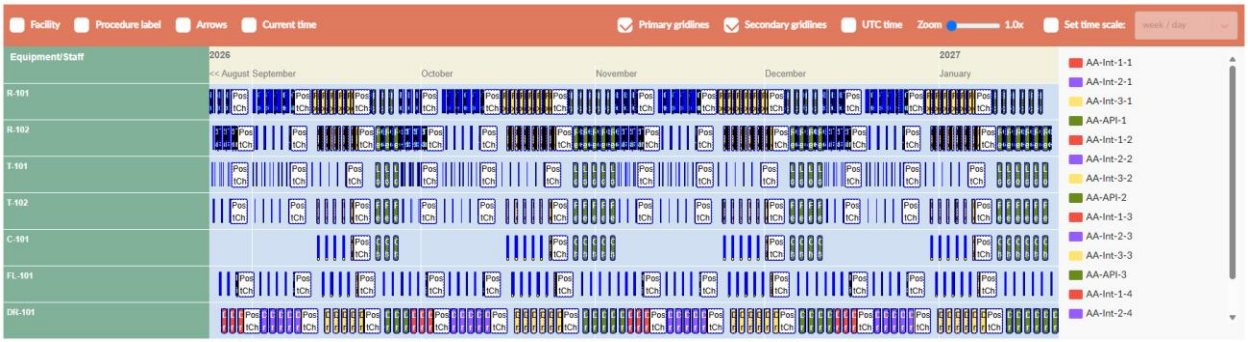


Figure 13: EOC for Case B: One Production Line; Multiple Small Campaigns for Each Step

Although Case B has a longer makespan than Case A, the final product is available sooner (i.e., it has a shorter time-to-market). Another advantage is that the in-process inventory levels are greatly reduced. This can be seen in the EOC and its linked intermediate inventory charts below. In this case, the in-process inventory never goes significantly above 2,000 kg. The use of multiple small campaigns rather than single large campaigns represents a scenario that is closer to a just-in-time (JIT) manufacturing plan.

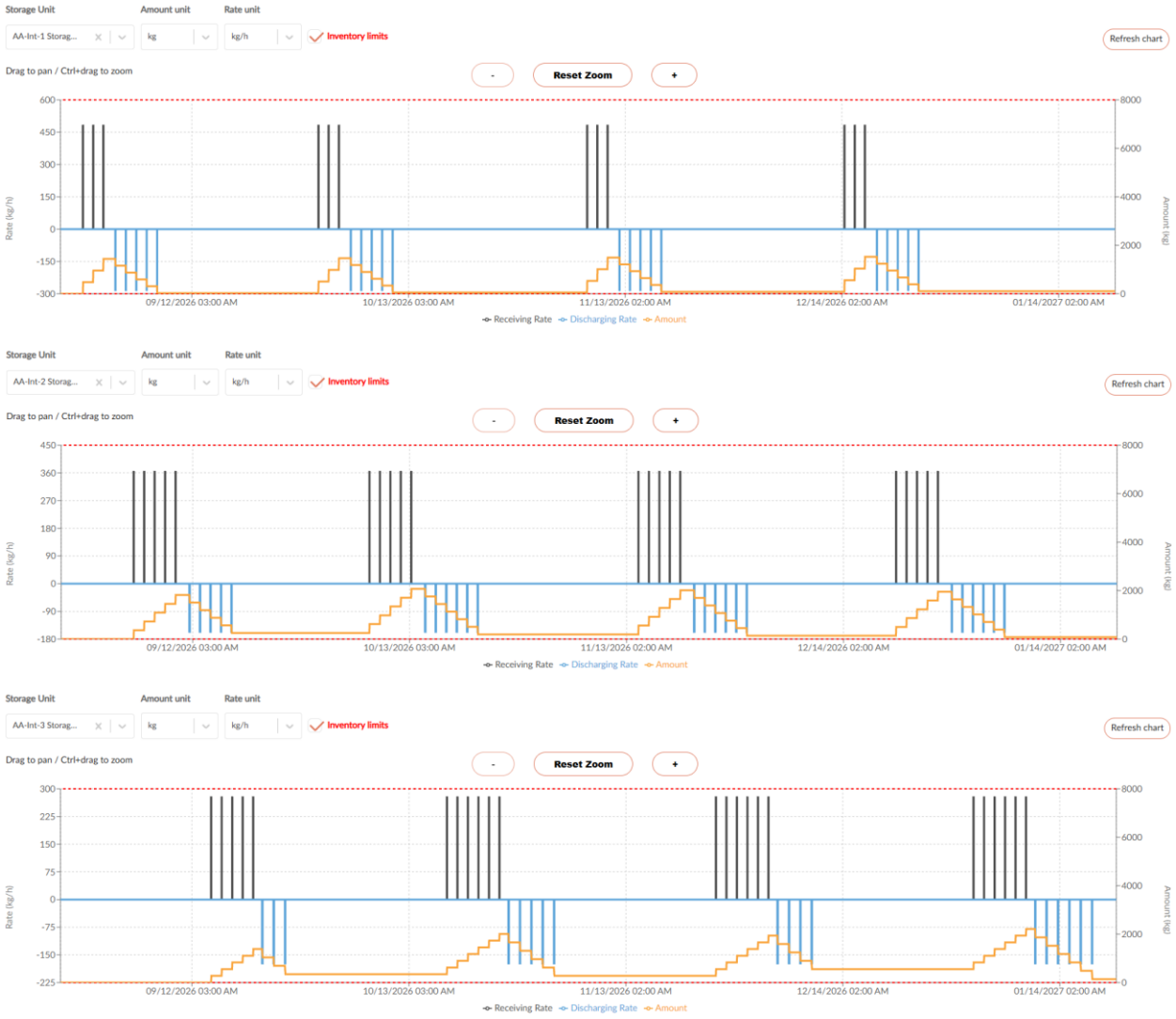


Figure 14: EOC for Case B with Linked Intermediate Inventory Charts

4 Case C – Single Large Campaigns, but Two Production Lines

An alternative production setup is to utilize multiple production lines to perform the synthesis. An example of this is modeled in Case C, which has two lines (denoted by equipment with a 1XX identifier or a 2XX identifier). In this case, Steps 1 and 3 are performed on Line 1, while Steps 2 and 4 are performed on Line 2. The utilization of multiple production lines in parallel allows the overall production schedule to be compressed since batches of Step 1 can be run on Line 1 at the same time that batches of Step 2 are run on Line 2, etc.

To do this, two new recipes were added to the recipe list, for step 2 and 4, utilizing the second line of the facility. Production templates for AA-Int2 and AA-API were created accordingly. Thus, recipes assigned to the campaigns in this case are:

- AA-Step1-Line1
- AA-Step2-Line2
- AA-Step3-Line1
- AA-Step4-Line2.

As a result, the makespan is reduced to only 10 weeks (see EOC below).

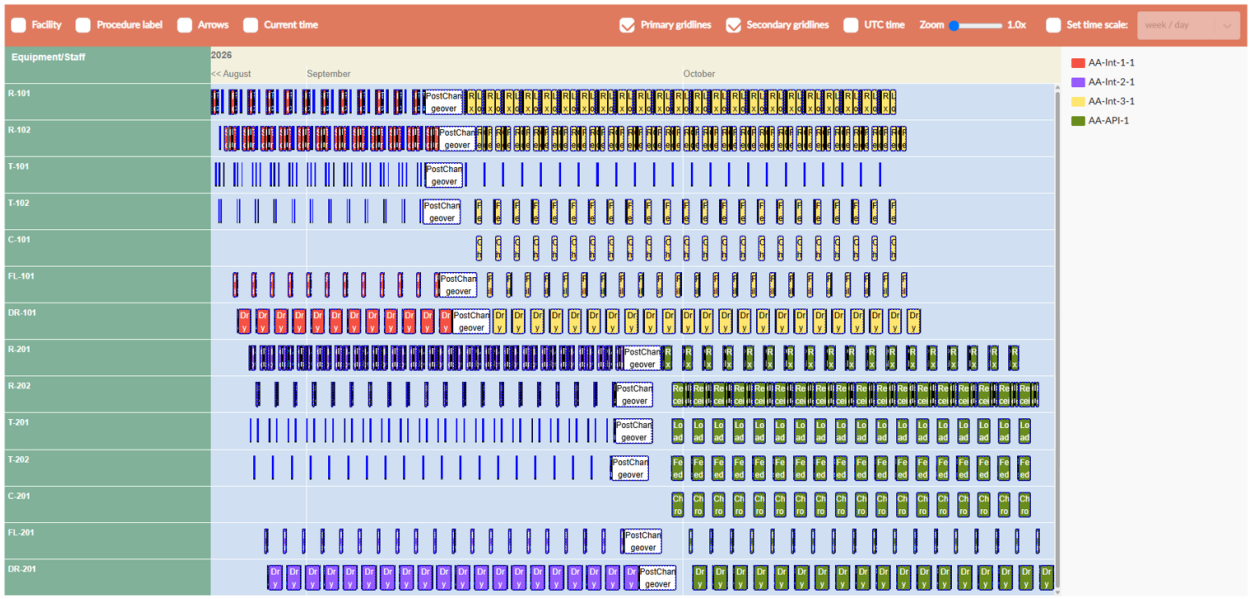


Figure 15: EOC for Case C: Two Production Lines; Single Large Campaigns for Each Step

The multi-line production strategy also partially alleviates the inventory issues that were associated with Case A because as a given intermediate is being produced by one campaign, it may be consumed by the subsequent step's campaign in a different suite. Due to the overlapping production and consumption of the intermediates, the highest amount of inventory for any component at any time is roughly 4,000 kg (although the combined inventory of multiple intermediates at a given time often exceeds this value).

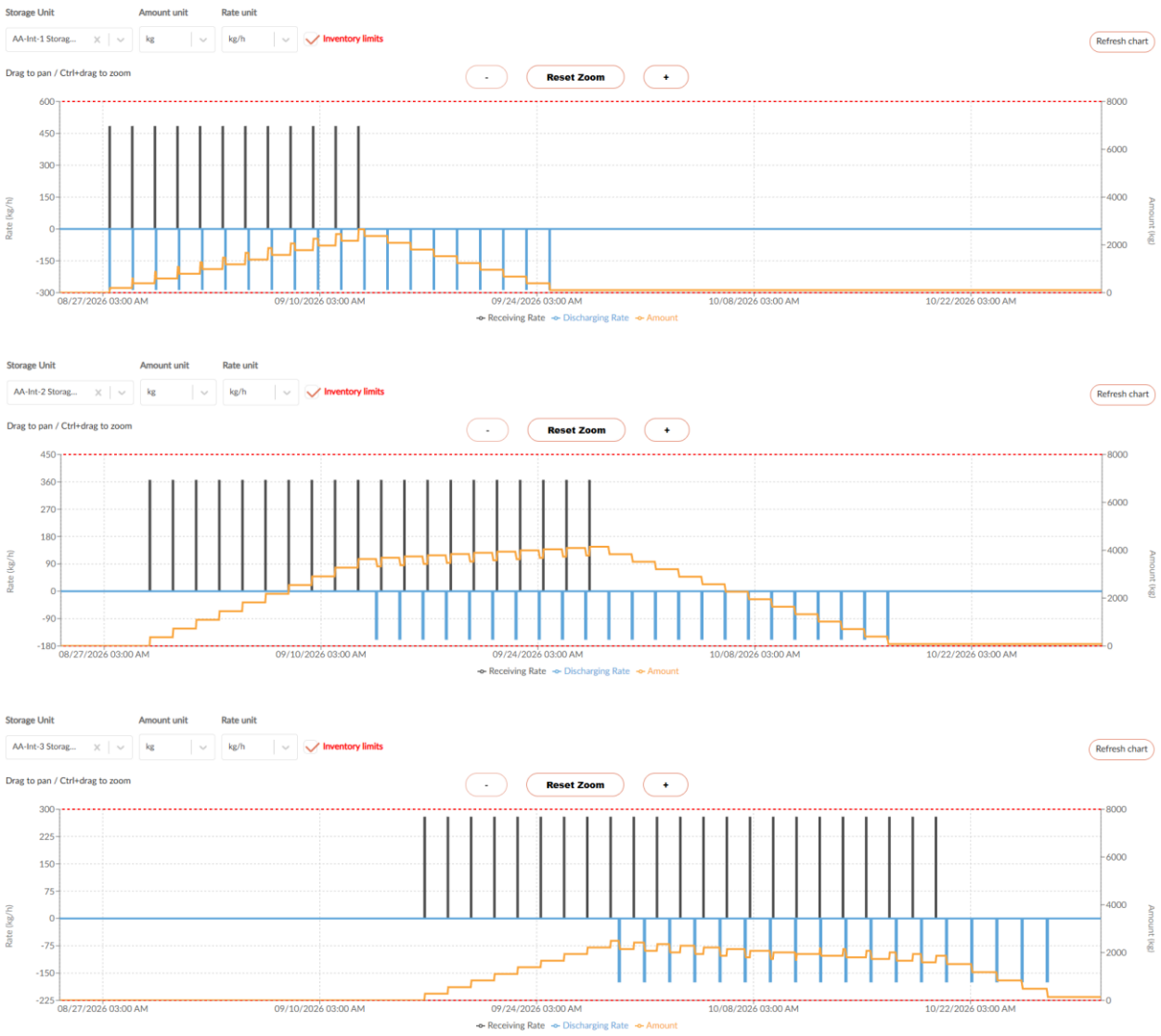


Figure 16: EOC for Case C with Linked Intermediate Inventory Charts

5 Case E – Tracking Labor Demand

In this case, four new recipes were created, in which specific operator labor levels have been assigned to various operations. The new recipes are:

- AA-Step1-Line1-Labor
- AA-Step2-Line2-Labor
- AA-Step3-Line1-Labor
- AA-Step4-Line2-Labor.

The Operator labor pool was created by selecting the facility's Labor node and adding **Operators** in the **Enter labor name..** input field. Unlimited persons was selected for the labor pool.

Once the operator labor pool was created, either one or two operators were assigned to most of the operations in each new recipe. This is consistent with a plant which has substantial manual labor. Highly-automated plants might require less labor. Note that the labor level for some operations remains at zero operators since there are some operations which are part of two different procedures (such as a Transfer Out from one vessel and its associated Transfer In to another vessel), and assigning labor to both operations would result in double-counted labor. Also note that fractional operators (e.g., 0.5 operators) *could* be assigned to operations if an operator can work on multiple overlapping activities at the same time (e.g., the operator could start a long reaction operation and then prepare a solution in a different vessel for a subsequent procedure while the reaction is proceeding).

The assignment of labor resources to operations may be done by visiting each operation in the recipe and add the relevant number of operators in the Labor tab.

After the labor assignments were completed for all recipes, the production plan was scheduled and the EOC was generated (see Figure below). Then the Labor chart was generated by selecting **Line charts**, and then **Resources chart** from the drop down menu. After selecting, **Resource type**, **Resource**, **Amount unit** and **Rate unit**, clicking on the **Refresh chart** button creates the chart.

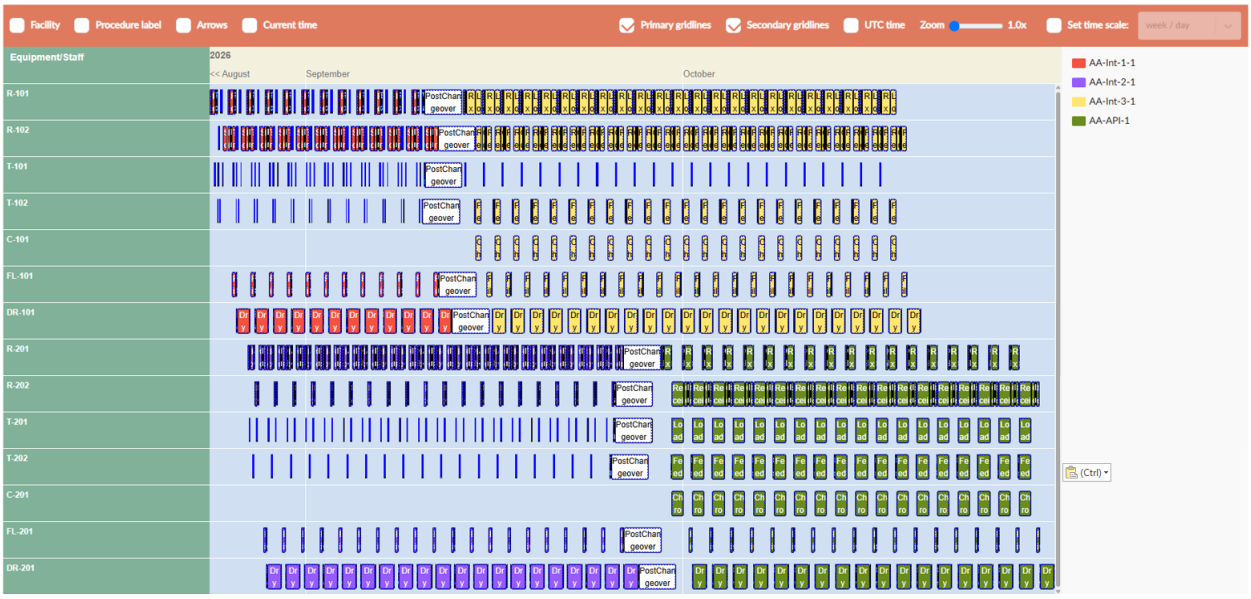


Figure 17: EOC for Case E



Figure 18: Labor demand chart

This chart shows that after the production plan begins, the average number of operators required by the process at a given time is around 7. However, there are large fluctuations in labor demand (typically between about 3 and 13 operators, although there is one point in time where 17 operators are simultaneously needed).