CLINICAL SUPPLY CHAIN PLANNING

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Transformation Happens Here

Clinical supply chain planning in life sciences is an increasingly complex process due to regulatory pressures, the time it takes to bring new drugs to markets, and internal dependencies on systems and non-clinical organizational support. At the core of most of these organizations are scientists who have become planners using Microsoft Excel. Data is scattered, vastly different by protocol, and lacking in integration across different sites, or contract manufacturing organizations (CMOs). Because the dosage, formulation, and state are still being finalized as an R&D activity, the data is constantly changing and isn't supported by the MDM governance programs required for ERP systems.

Having planning processes that can run at a program level across multiple trials and understand each trial's contribution to the program is imperative to maximize the understanding of the efficacy and safety of new candidates and optimize the benefits to prospective patients by improving speed to market in a safe, qualified manner. Planning each protocol requires an understanding of:

1. The purpose of the trial
2. Specific patients' eligibility to join
3. How many patients will enroll (timing of enrollment and assumptions around longevity
4. Combinations with other drugs
5. Frequency of dispensation
6. Dose and form
7. Efficacy/safety

The end-to-end planning for a clinical trial program requires companies to develop a target operating model (TOM) or blueprint for how to effectively plan for this inherent complexity given the unknown nature of the supply chain. The core TOM is similar to its commercial counterpart but with some nuanced considerations that alter demand/supply balancing:

- Data management requires the continuous monitoring of ever-changing data. Best practices involve appointing lifecycle managers to facilitate timely and accurate data management
- Demand planning is based on planned enrollment dates with the number of patients, test groups, and sample sizes within each test group

- Supply planning requires estimates of material availability and, for biologics especially, an impact on shared equipment with commercial as well as an integrated plan with CMOs
- Distribution requirement planning requires collaboration with 4PLs over customs/shipping/logistics concerns be aligned early to prevent changes that may have impacts on the product between the depot to the clinic.

These process nuances require specific capabilities that best-in-breed planning systems need to support.

Any advanced planning system (APS) should have the following 12 clinical planning capabilities:

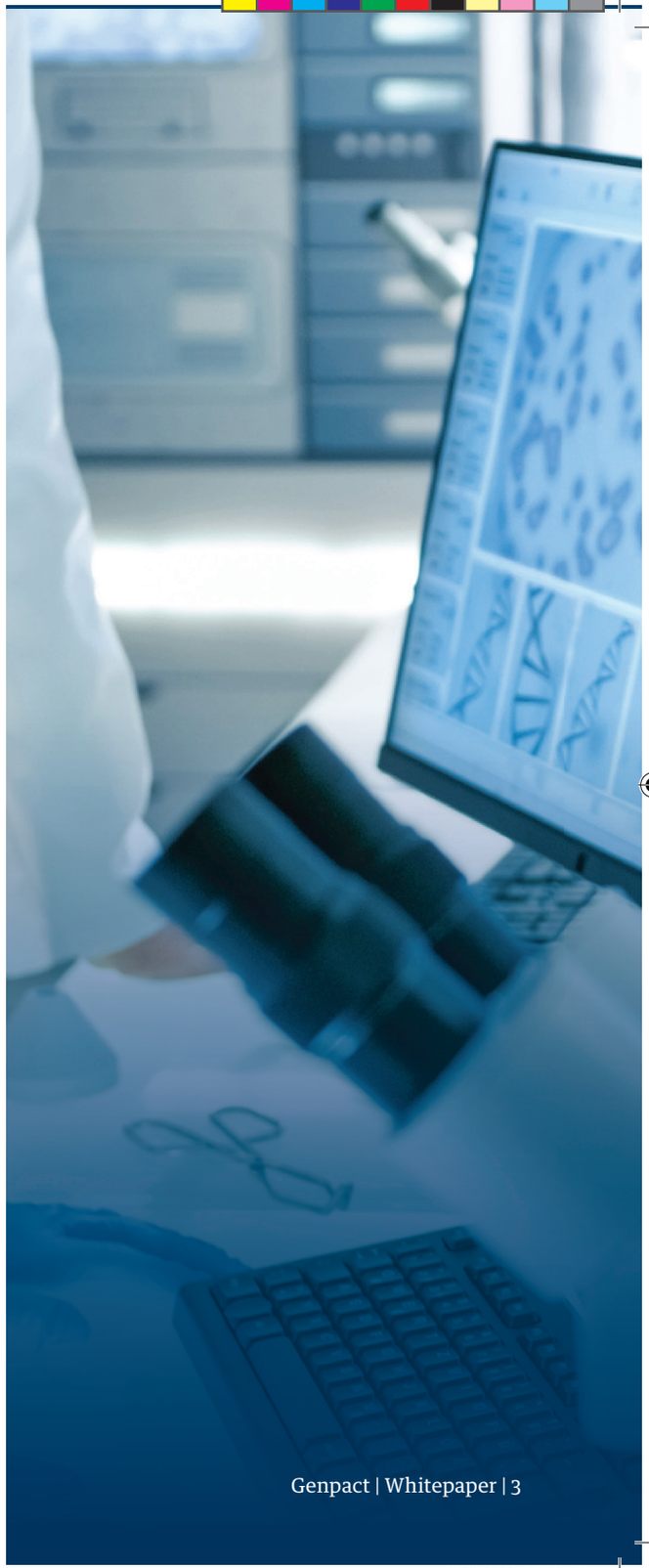
1. Agile lifecycle management (LCM) processes that include supply chain master data management
2. Program review as part of the clinical sales and operations planning (S&OP) process
3. Underpin all supply chain nodes in a single environment, even if components of the supply chain are sourced in dif-ferent instances of the ERP system
4. A study design (including double-blinded) that is scalable to meet country-specific approval dates
5. Calculated demand curves based on study design
6. The ability to update demand and include internal R&D activities in the demand picture
7. Incorporate both clinical and commercial nodes of the same supply chain in a unified, transparent fashion
8. Manage regulatory approvals by country and balance demand and supply with jurisdictional approvals
9. Incorporation of stability protocols in the supply review
10. The ability to manage comparators effectively
11. Manage 3PL and 4PL partners in a way that is commensurate with the relationship
12. Customized KPIs and reporting

These key capabilities are outlined across the different stages of the TOM below and highlight best practices to consider when deploying a clinical planning APS tool.

Data management

Data management is a challenging, ongoing process that requires precision over years of changes to the data as a molecule progresses through trial stages. A complete material master data, bill of material (BOM), and network build are crucial for accurate planning.

In early-stage trials, the SKU data and BOM data maturity data are low. Planning is taking place at a high level over a long-term horizon. It is important to identify and maintain the essential attributes to enable top-down independent demand propagation and initial supply response with allocations of capacity. This pro-cess needs to consider the trial timeline and identify when master data requires updates. This will ensure that as a study reaches new phases throughout its lifecycle, data maturity will enable other processes with the right quality all the way through to near-term execution when the data has to be accurate for planning and regulatory reasons.



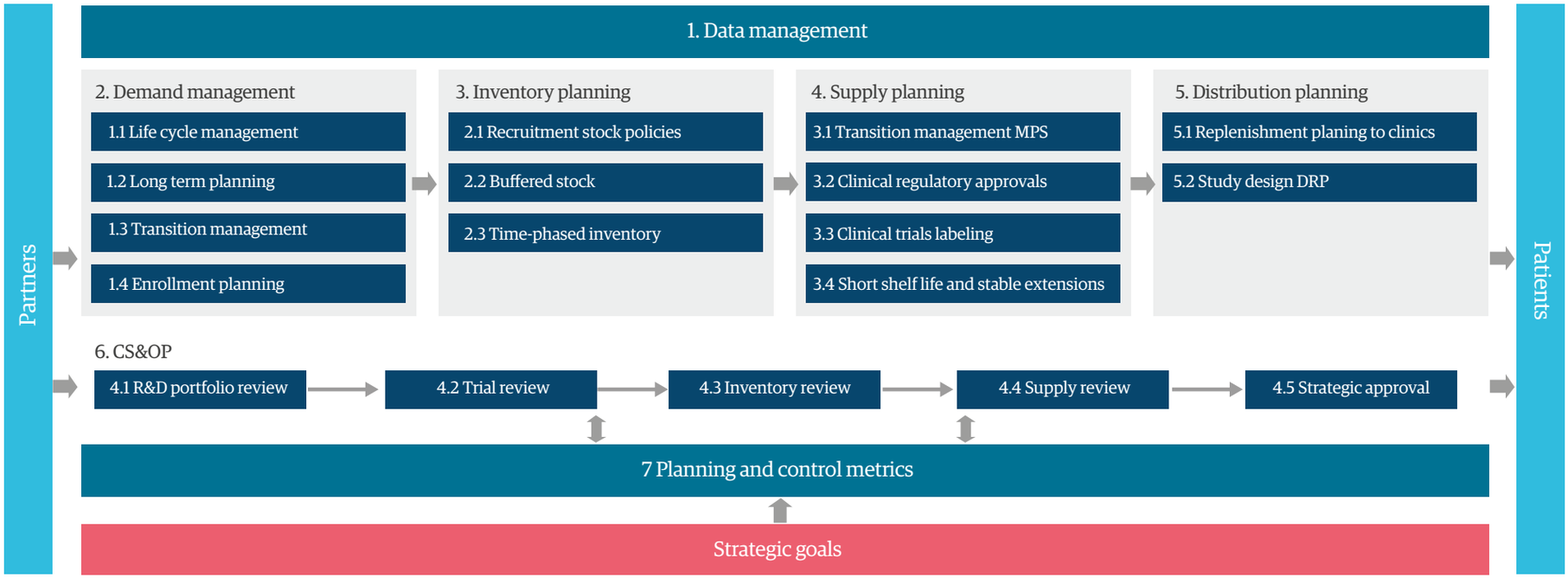


Figure 1. TOM for clinical planning

Demand management

The demand management process is based on planned patients' enrollment or placeholder demand (through planning BOMs) depending on the phase of each study's approval. LCM is the first step in this process. This is an ongoing process with continual iterations that require precision in executing the right changes at the right time. This will ensure that demand calculations can proceed from a long-term strate-gic plan (ideas not yet approved for studies) to a near term execution window in which studies are ap-proved and have real demand. Following the project initiation until the study is approved internally, demand planning is based on assumptions of the total number of patients to be recruited in a given market. At this stage, long-term planning is typically set up as planning materials at the study level. After internal compa-ny approvals, there is a transition to execution SKUs, and the forecast shifts to a clinical trial forecast. After study initiation the forecast will become independent demand with confirmed patient enrollment shared by local entities coordinating that activity. The execution process is then taken over by the ERP system.

Inventory planning

For clinical trials, the service level is always set to 100%, and there is no room for delays or late fulfill-ment. Inventory planning and time-phased strategic stock levels are key to achieving that service level. The key variable and starting point for inventory-level setup will be planned recruitment completion. Supply managers responsible for setting the right levels will tend to keep higher stock if recruitment is yet to be completed to prevent volatility, enrollment acceleration, or general increases versus planned forecast. Throughout the course of the study (and after the first patient receives the first dose of the product), stra-tegic stock needs to be specified as demand/and supply stabilize and becomes less variable. Using time-phased inventory will support the project ramp-down with last patient/last visit, minimizing inventory that will expire.

Supply planning

The supply planning process has a strong correlation to LCM. Most of the steps within master production scheduling activities, including supply propagation, supply-to-demand allocation, and the firming up of planned orders are equivalent to the commercial drug business processes. Accordingly, supply planning will typically take place on a planning material, including firming of planned orders. This part of the process should be fully handled in APS without interaction with ERP systems. When approval is in place and actual material is created, with the right maturity of master data, firm orders can be transitioned and integrated into the ERP system for execution. Nuances in supply planning processes include:

1. Blinding the supply plan where different SKUs in the study are packaged together as to be indistin-guishable
2. Stability programs where R&D is planning to extend the shelf life at different markers to be able to plan supply from the initial and fast-to-expire products to a more stable supply plan with less im-pactful expiry
3. Accelerated release where the next level of the BOM may be completed prior to when the long lead time testing results are achieved

Distribution planning

The key focus of distribution planning is to make sure that products reach the clinical sites where actual dispensation to patients is taking place, on time. Firming of distribution orders is equivalent to firming MPS for make/buy items, where availability of the supply needs to match the demand due date. To mitigate the risk, in-transit stock should be added to inventory and considered in the netting of available supply. While building a distribution plan, the study design must be considered to buffer risks in the execution phase through strategic and/or cycle stock.

Clinical S&OP

The clinical S&OP process in R&D departments is the same as commercial drug production, with a month-ly cadence. In commercial pharmaceuticals, the S&OP process is typically at the brand level, whereas in clinical S&OP, the review takes place at the program or even study level. The clinical workflow typically has five steps:

1. Program review
2. Demand review (trial review)
3. Inventory review
4. Supply review
5. Approval (single approval for clinical)

Planning and control metrics

Planning and control metrics support the current-state assessment of day-to-day work as well as decisions across the whole clinical S&OP process. APS tools can customize dashboards and scorecards to meet the clinical business across a range of KPIs. These typically include:

1. Regulatory date changes by country
2. On-time, in-full to net requirements (demand)
3. Strategic stock attainment
4. Expiry risk
5. Capacity utilization

All of these unique nuances in clinical supply chain planning mean no out-of-the-box APS exists to meet clinical trial requirements. To overcome this, life science organizations are increasingly partnering with service providers to design a digital clinical trial solution that works with existing APS tools.

The APS capabilities required for clinical supply chain planning

The lifecycle management process

The lifecycle management (LCM) process is extremely challenging for clinical programs because the time from trial inception to execution can take years, but the precision required to convert data from planning to execution data at stitch points is discrete.

As an example, for an unapproved trial, a full material BOM and supply chain network of how and where the product will advance is not known. At this point in time:

- Planning materials/BOMs and sourcing rules should be led by the APS platform to be planned ap-propriately but the trial is not ready to move into execution mode
- The APS platform should have the ability to quickly create the extended network inclusive of clini-cal finished goods, drug product, and drug substance levels based on templates and include stra-tegic real raw material numbers for a purchasing plan
- Demand is based on global estimated patient doses on the clinical finished good as forecast and dependent demand explosion would occur through the extended BOM to the lowest levels
- The supply plan would be unconstrained because not enough data is known for the site, equip-ment, or process area in which manufacturing will occur

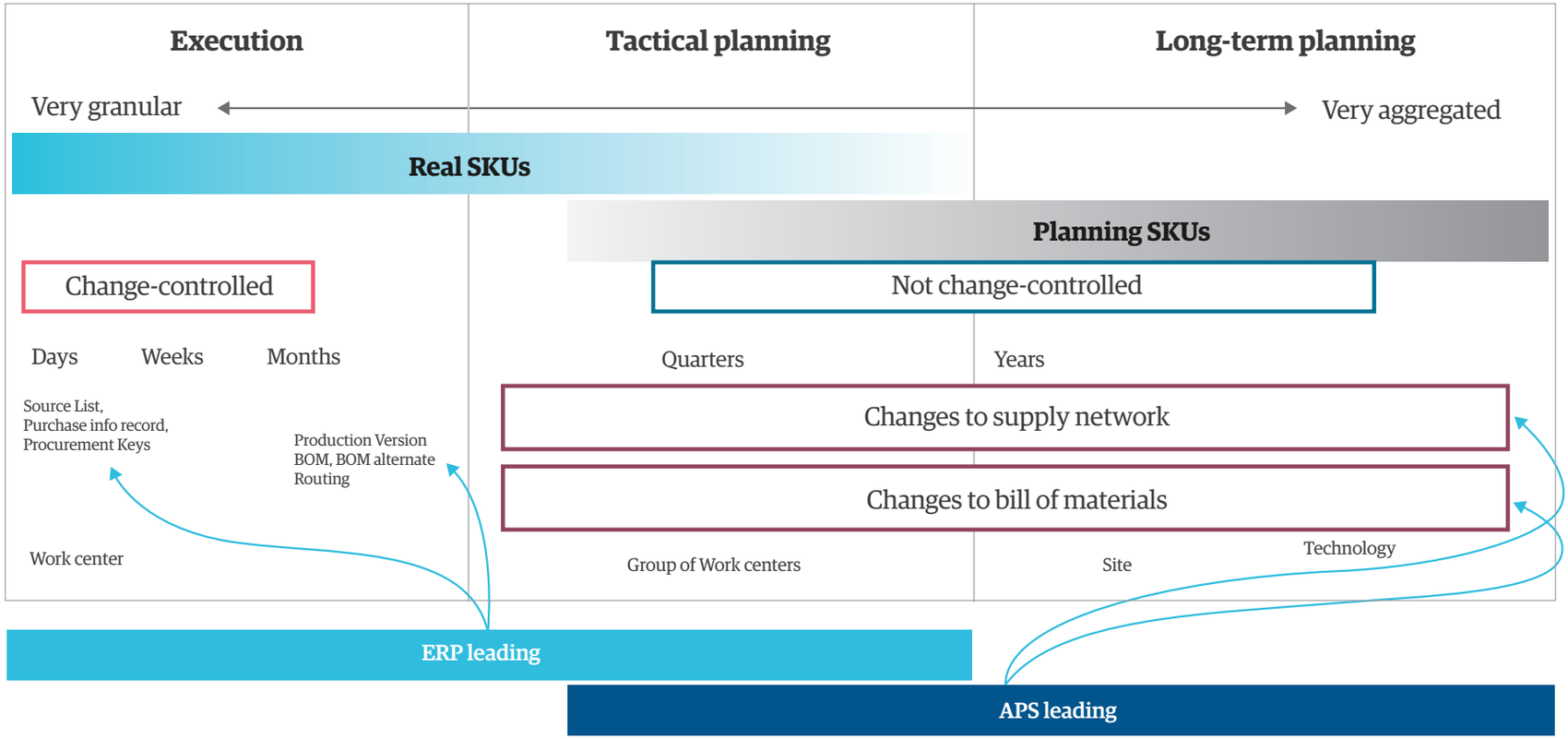


Figure 2. Lifecycle management horizon with master data management required

Fast-forward to the point where the trial has been internally approved to proceed, but full regulatory ap-proval is still to take place. At this point in time, based on the long lead times of the drug substance:

- The real material numbers are created with time-phased regulatory plans to approve this
- The lifecycle manger would stitch the supply chain at the key transition point to have the ERP sys-tem create the drug substance as a source for the planning material at the drug product and clini-cal finished good levels
- The demand may migrate to understanding which countries are participating in the trial, the test groups, and how many samples are in each group so the demand may be updated to accommo-date these known data points with the dependent demand still propagating down to the real drug substance SKU
- The drug substance at this point can be limited to the line/process area/ bioreactor at the drug sub-stance level that would limit the volume throughput

Fast-forward again, to the point where we have real ERP SKUs from clinical finished goods through all levels of the BOM. The previously stitched network is updated again, this time with data from the ERP system. The lifecycle manager ensures that the network is in place and demand is now flowing from a clinical forecast based on planned patient enrollment. The supply plan is now developed including planned regulatory approval and expiry dating with material availability in a constrained situation.

The capabilities the APS tool needs to execute this LCM process include:

- Templates to create planning tools quickly
- Workflows to monitor and approve master data management
- Alert options. This should be automated so that when an ERP SKU comes into the APS tool, it can automatically stitch the supply chain and communicate to the lifecycle manager what has been done to minimize the risk of supply chain disruption
- Simulation capabilities. These should allow clinical planners to change approval dates by country, patient enrollment dates or quantities, supply source lead times, and constraint data. Impacts on the ability to meet the patient need by date should be highlighted so that planners can take appropriate actions to ensure that supply is not impacting a trial requirement

The clinical S&OP process

Clinical S&OP processes review large, long-term programs in terms of the granular detail of the near-term clinical trials executed. The long-term view looks at the total investment in R&D by trial stage against the broad spectrum of the portfolio (for example, oncology phase 1 trials versus cardiology stage 4). The most balanced portfolios will be the ones that can achieve steady commercialization to help the most patients worldwide.

The review at the program level should be based on a 10-year view of CapEx investment to procure the right equipment at the right manufacturing site, qualified ahead of the time required to produce product for that trial. Make-versus-buy decisions should be discussed early on so that brick-and-mortar changes can be executed ahead of time. The program review should be conducted quarterly, and updates should be passed along to the trial review with any changes. Metrics for the program review should include:

- The total number of programs underway
- The trial stage of each program
- The number of trials planned
- The total dollar investment planned
- The amount of money spent against the plan

Clinical trial review

Clinical trial review is analogous to a demand review on the commercial side, with a focus on capturing an accurate patient enrollment plan for that trial. The culmination of all the trials provides demand at the active ingredient/drug substance level, all the way up to the clinical finished good level by country.

Specific trials will need to be added to the demand for R&D use for stability or sampling, and internal de-mand should augment the forecasted patient enrollment demand. Each country has an approval date for the trial in which the planned enrollment takes place after the planned enrollment date. As patients are en-rolled, the actual numbers are treated as independent demand that should consume the forecast. The de-mand review should be performed monthly and capture metrics on planned patient enrollment by country and time bucket, the number of changes to approval dates, and actual enrollment as a percentage of the plan. The trial review then passes the output to an inventory review.

Inventory review

The inventory review should look at planned and actual enrollment and determine how much inventory should be stocked at sites, depots, and/or clinic sites at the trial level. The inventory stocking plan should be time-phased, ramp up ahead of the planned enrollment period, and ramp down as the procedure devel-ops and the enrollment is more predictable in execution mode. Items with shorter shelf lives should carry less inventory on hand and plan for more use of global pools than items with longer shelf life that are more established.

Due to demand risk, strategic stock should augment variability-calculated safety stock so that every pa-tient enrolled in a study receives the treatment at the prescribed time despite the expiry risk that this pre-sents. Global studies require better planning to spread this risk across many countries to better utilize inventory and improve the data the trial is generating. This type of postponement strategy can effectively manage long-lead-time items with a variable demand signal and buffer to the global supply needed.

The inventory review should be executed monthly based on net change adjustments from the prior period. Key metrics of the inventory plan should be:

- Targeted enrollment coverage
- Strategic stock risk coverage
- Expiry risk by country/depot

The inventory plan creates additional demand, which along with the demand plan should be passed along to supply review.

Supply review

The supply review will be performed monthly as a response to demand and inventory plan approval. It will net the requirements and determine how many batches will need to be supplied at the drug substance, drug product, and clinical finished goods levels.

Lot sizing is typically adjusted based on trial phase and planned based on:

1. Yield
2. Sampling requirements
3. Approval dates
4. Usage in the clinics
5. Distribution to the depots

The metrics for clinical supply planning should include:

- Nettable grams of API equivalents by time bucket
- Percent of planned usable product pegged to demand/inventory requirements
- Percent of supply that pegs to expire. This is a key difference in clinical planning compared to commercial planning. It is prudent to cover more inventory as a common metric is 25% of the sup-ply will expire

After the supply review is approved, the one total operating plan for clinical will be sent to leadership for review. The approval takes place with leadership reviewing the approved plans that are intrinsically linked to each other. Various questions will arise that typically include changes to trial dates while ensuring that the inventory doesn't expire based on those changes. Today, leadership is looking to ensure 100% of pa-tients receive treatment as planned and the progression from near-term outward.

With this approach, clinical S&OP planning really ties to clinical S&OE activity. The migration of this pro-cess should start with the long-term plan and work forward. This will tie the CapEx investments required in the portfolio review all the way to near-term exceptions that are impacting the short-term plan.

APS tools should be able to seamlessly convert program-level data to trial-level data, balance demand, inventory, and supply, and execute clinical S&OP processes in a repeatable, timely, exception-driven manner while answering key questions from leadership.

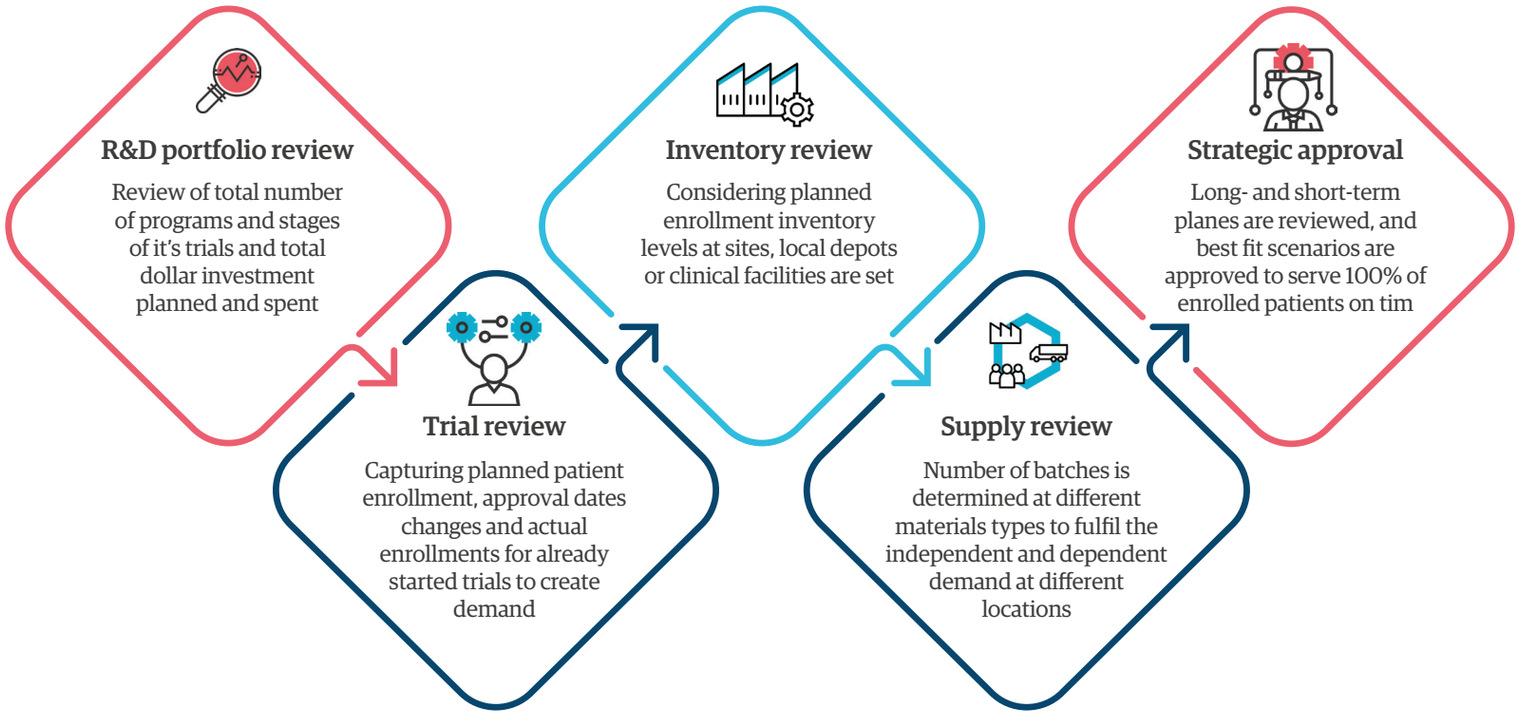


Figure 3. The clinical S&OP process

Integrated planning

For most pharmaceutical companies, data is sourced across different ERP systems in various custom applica-tions and/or Excel. The data model is not comprehensively part of any ERP or APS system. Couple this with commercial counterparts who often have different ERP systems, and building out an integrated network from a clinical viewpoint can prove extremely challenging.

Take biologics in clinical planning, for example. The typical network may start at a depot and drive down to clin-ical operations for pack and label, a drug product level on a commercial production line, and a drug substance site in commercial, in addition to using the bioreactor. The supply chain network in today's often siloed opera-tions requires collaboration between clinical planners and two different levels of commercial planners.

APS tools should be able to view the network, stitch together where commercial and clinical connect, and share raw materials through a common dependent demand signal, all while determining one plan for the entire network. Planners should be able to share information and make collaborative decisions based on known assumptions and view the impact of these decisions. These key interactions should be archived with the ability to retrieve them upon user request.

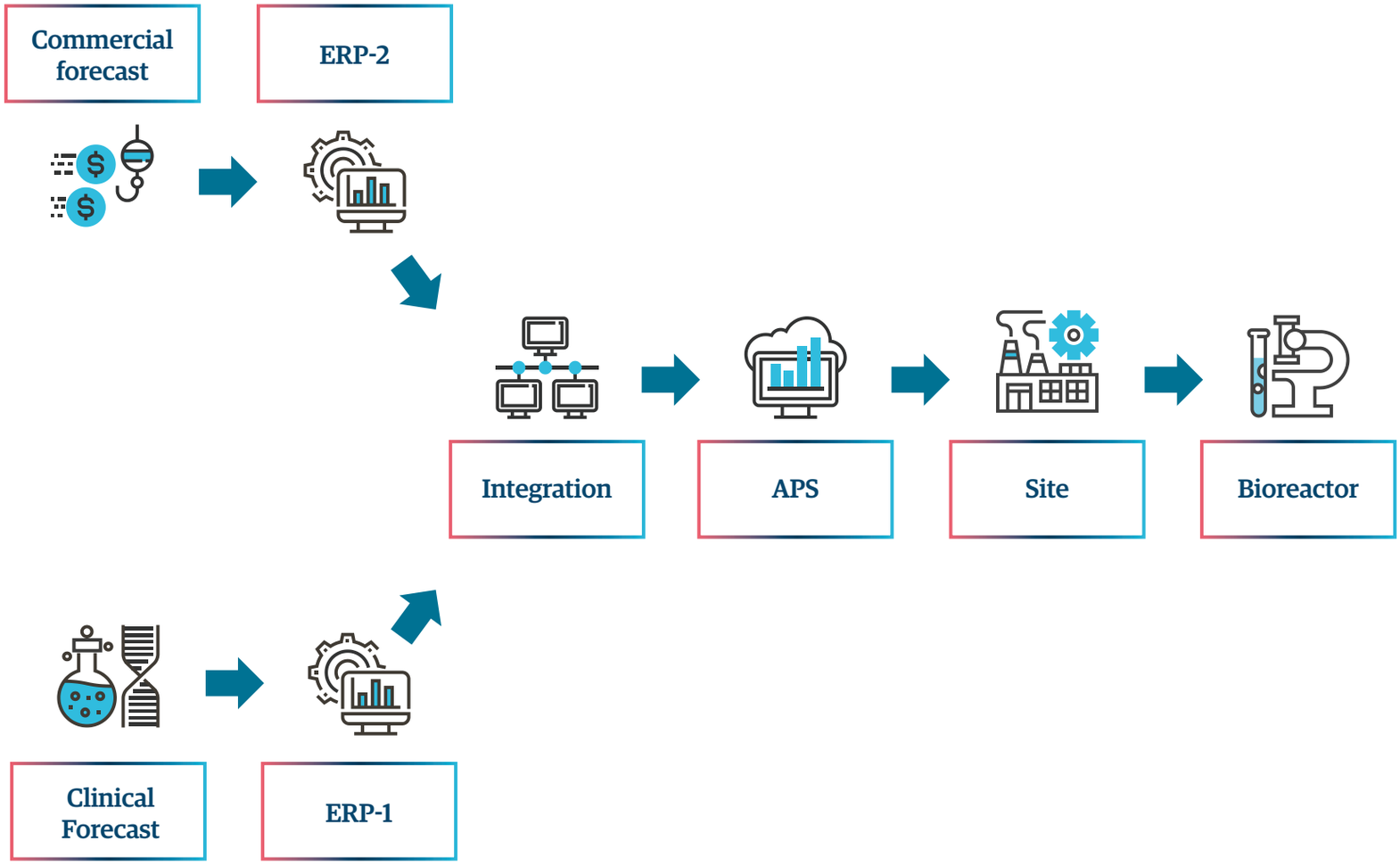


Figure 4. Integrated planning in practice

Study design

The study design has different impacts on demand, outlined below.

Study type	Description	Effect on demand planning
Double-blinded	Neither the patient nor the practitioner knows which treatment group the pa-tients are participating in	Consider each patient belongs to each treatment group. Demand will be over-stated to count each patient for each visit as if they are receiving all treatments
Titration	Study that increases the dose for each patient over time	Demand will be a ramp up over time for each site as the trial proceeds
Dose escalation	Trial to determine that maximum ac-ceptable dose	Demand will be a ramp up over time for each site as the trial proceeds with peak demand unknown as well
Crossover	Trial in which patients switch treatment groups at a specified time	Time-phased mix of demand has to be account-ed for by aggregating patients to the cross-over point dates
Adaptive	Study that can alter the specific treat-ment protocols mid-trial to improve ef-fectiveness for individual patients	Planned variation in demand to be built into models. Best use of make-to-order scenarios with buffered inventory at DP levels
Placebo-controlled	Trial in which the control group lacks an active ingredient	Additional SKU to be considered as demand that requires a different manufacturing build with alignment to expiry SKUs that contain the active ingredient
Multi-country	Trial that maximizes population variation by spanning the trial across more than one country	In addition to study demand dates, country spe-cific approval dates create country level timing of demand based on local regulatory approval

APS tools should have the ability to select the different study design type and then dynamically change the inputs so the study design can be accurately planned.

Double-blinded studies, in which neither the patient nor the supplier knows which treatment was given, requires this unknown to be built into the delivery functionality. A double-blinded BOM mimics the groups in the study with a quantity per assembly of each possible group can be created. In this manner, the double blinded BOM can act similarly to a traditional sales BOM. The order is placed from the clinic site onto the depot for monthly replenish-ment for trial 123. Trial 123 has one placebo and three different doses. Each dose plans to support five patients at the clinic, and the placebo is expected to be used twice. The replenishment order would be created based on a double blinded BOM of 2/17 for the placebo and 5/17 for each of the test groups. The value of setting the data up in this manner means it is not possible to determine which patient receives which dose or if they receive a place-bo, thereby supporting the study design required for a double-blinded study.

APS tools should be able to accommodate not knowing the full complement of the supply to support an individual patient's random assignment. Therefore, the demand cannot be an independent sales order that specifies the part a patient would receive.

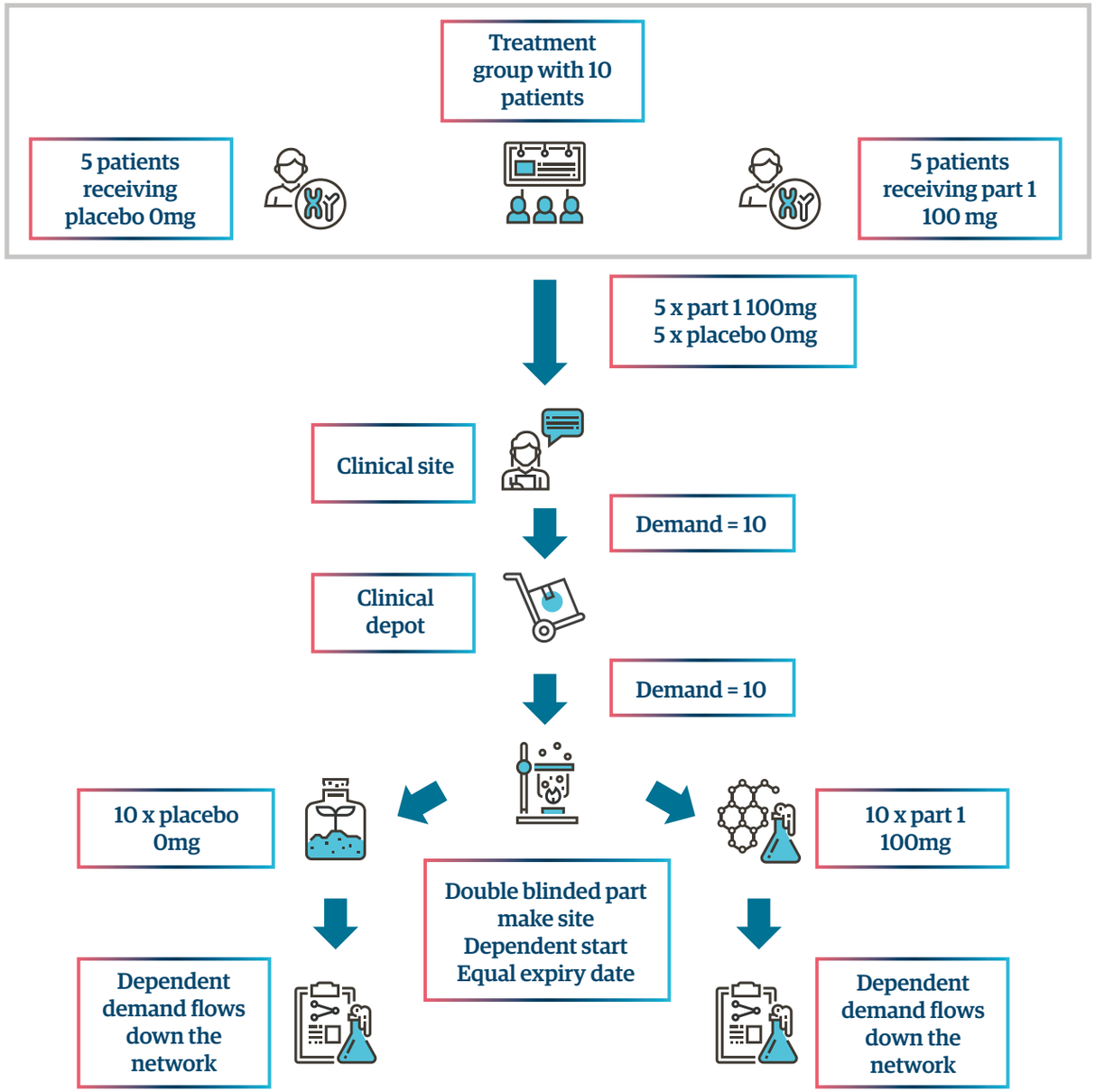


Figure 5. Impact of study design on demand

Calculated demand curves

Demand data models

Clinical demand requires a unique data model. Field names and descriptions can be seen below.

Field name	Field description
Program/project	Identifier to recognize the overall arching program/project as the study defines it
Program status	Indication as to whether the program/project has been approved to proceed
Study	A specific study/trial identifier, which will link a study/trial to the program
Study phase	Phase I, II, III, IV: This is for informational purposes and can help identify the degree of changes and common attributes associated with the study's design
Therapeutic area	Indicates which area of a given candidate's disease (for example, oncology) will be subject to study
Treatment groups	The number of treatment groups and controls used to calculate total patients and demand at each group
Number of treatments	Quantifies how many times a patient will take the treatment
Dose	Identifies the quantity of active ingredient that a patient will receive with each treatment
Repeat visits at dose	Identifies how many times a patient will receive a specific dose
Attrition rate	The estimated number of patients that may not complete the study
Languages on label	Identifies which language will apply to specific labels
FPFV	Date of first patient first visit
FPLV	Date of first patient last visit
LPFV	Date of last patient first visit
LPLV	Date of last patient last visit
Quantities per pack	Identifies how many treatments are in each package

These fields are required either for informational purposes as part of the header record or as specific inputs that go directly into the demand calculation.

Demand calculation

APS tools should calculate demand following these steps:

1. Inputting header attributes. Clinical demand is calculated at the program, project, and study level. Each study will have its phase of trial and therapeutic area defined
2. Select the countries in which the trials will be planned. Each country will have a predefined depot and number of site linkages. Additionally, each country requires regulatory approval for that trial, which may be different from the study's as a whole
3. For each clinic, the study design protocol will determine the number of patients to be enrolled and should also have the dates pertaining to FPFV, FPLV, LPFV, and LPLV
4. Lead time definition. Lead time between depot and sites, the latest release time for when the kits must be available at the site, and buffer time to account for any unplanned delays
5. Group countries that should have the same labels. Each label's language will have the same CFG material
6. Grouping the same language and label by country will define the quantity that each country should receive and distribute to local clinics. The grouping will include items for blinding so pharmaceutical and clinic representatives are not aware of which product each patient received
7. Define the do-not-dispense period as a lead time so the product cannot be used, even after receipt
8. Within the same language labeled on a pack for each country, multiple treatment groups (meaning doses) can be defined. The distribution ratio of patients between the treatment groups must be entered (for example, five different doses at 20% for each dose)
9. Define the treatment period and the treatments that this study is to carry out. The treatment period should contain the number of visits, the minimum gap between visits, and the dosages. This will provide the demand in units for each treatment period
10. During the trial execution, there is the possibility of patient attrition. This rate can result in the patient leaving the study or moving to another treatment group. For example, a 25% attrition rate for a study of 100 patients would require 125 patients to enroll. If a patient transfers to a new group, then an additional patient may have to backfill the original group depending on the study's design
11. After the clear definition of the treatment group, the phase of the trial, and the treatment period, create a matrix to assign each of the treatments to the phase, treatment group, and treatment period. These inputs will allow for a calculation of the units needed for each treatment group and each treatment period
12. Determine a buffer stock of inventory at the clinic sites and depots to cover supply variability and risk. For each country and material, define the time-phased safety stock needed at any particular date. This quantity may be a calculated range based on demand or manually determined and inputted by the clinical planner

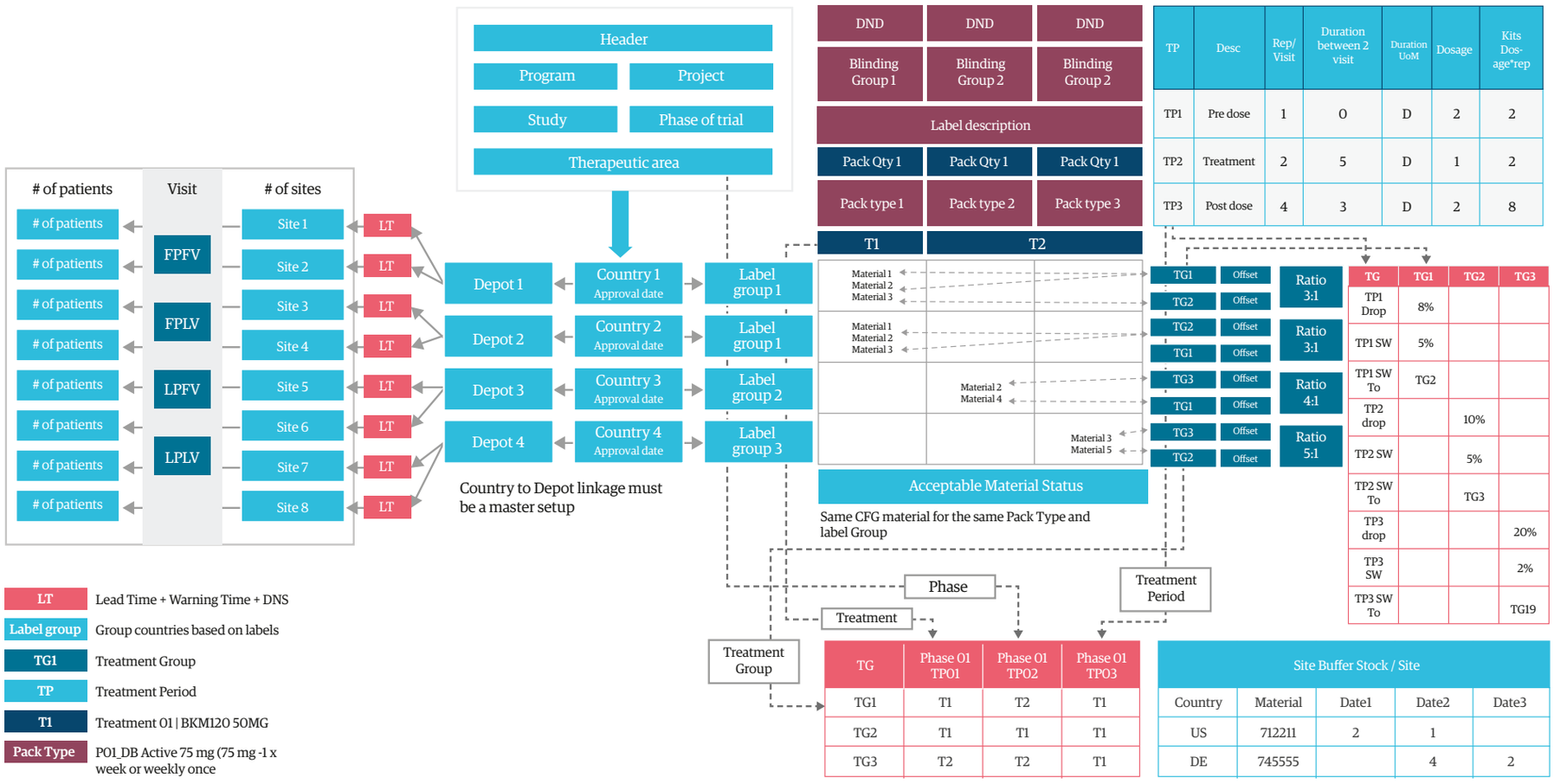


Figure 6. Clinical trial inputs for demand generation

Demand can be calculated for each country based on the five enrolment types:

1. Linear enrollment (100/0): Split the total duration between FPFV and LPFV into two halves by calculating the median. All patients enroll in the first half
2. Linear enrollment (75/25): Split the total duration between FPFV and LPFV into two halves by calculating the median - 75% of the patients enroll in the first half, and 25% enroll in the second half
3. Linear enrollment (50/50): Split the total duration between FPFV and LPFV into two halves by calculating the median - 50% of the patients enroll in the first half, and 50% enroll in the second half. This is basically a true linear distribution of patients over time
4. Linear enrollment (25/75): Split the total duration between FPFV and LPFV into two halves by calculating the median - 25% of the patients enroll in the first half, and 75% enroll in the second half
5. Custom enrollment: Prepare a visit schedule for each patient. Calendar dates are marked with the number of patient visits on a particular date. This type most often occurs when there is a prolonged period of time over which there are challenging determinants for patient enrollment (for example, in oncology studies)

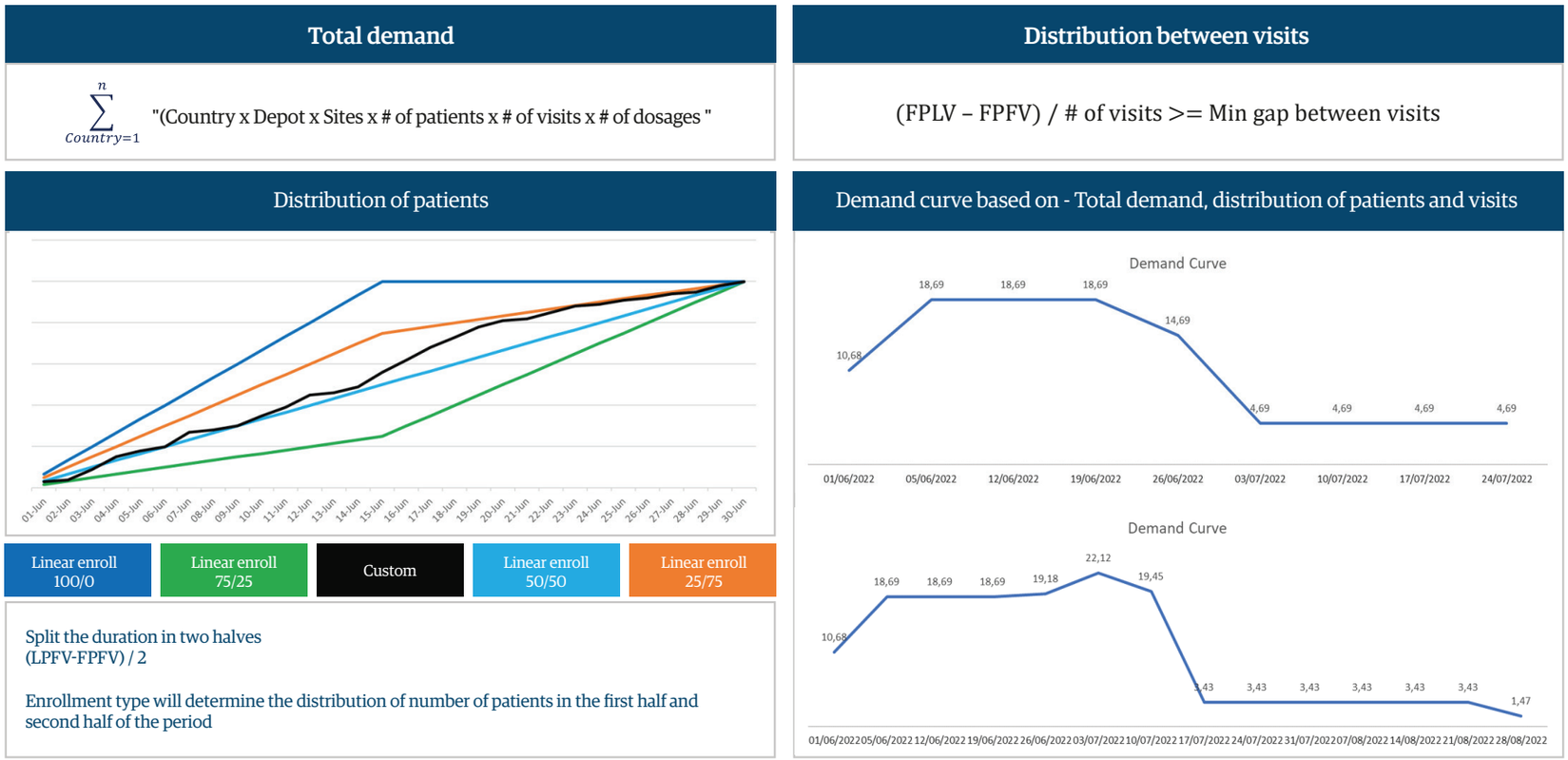


Figure 7. Clinical trial demand forecast values

Total demand can be calculated as

$$\sum_{Country=1}^{n} \begin{pmatrix} Country\ x\ depot\ x\ sites\ x\ number\ of\ patients \\ x\ number\ of\ visits\ x\ \ number\ of\ dosages \end{pmatrix}$$

The study design will determine the minimum gap between two visits. Therefore, check to ensure this constraint is respected and adjust the dates if the output of this validation is false.

$$\frac{(FPLV - FPFV)}{\#\ of\ visits} \geq Minimum\ gap\ between\ visits$$

Demand may also include internal demand at any level of the BOM that may have to be aggregated according to patient enrollment demand.

Internal demand considerations

Internal demand can cause significant deviation from the baseline from a demand stability perspective. These demands can come from sampling to be used in R&D labs, stability protocols to assess shelf life, or as tests to be used in laboratory experiments. This demand may also be at any level of the BOM.

The best practice process is to differentiate a demand type and plan for it as if it were independent demand. The internal demand should be aggregated with the enrollment demand to calculate total forecasted demand. If the network is built out and connected, then this demand will cause a BOM explosion throughout the extended BOM. For example, if R&D is using tablets at the drug product level for a stability program, the BOM explosion would happen through the drug substance level and aggregate the demand so the correct number of batches would be included in the net requirements calculation.

This demand can be viewed as a forecast prior to when the study enters execution mode, but as actuals after a study has gone live. If forecasted, the internal goods issue from inventory would drive the consumption of the forecast. If the extended BOM is not yet set up in ERP systems, planning materials following the lifecycle management process should be followed where the demand flows from the planning DP part to the DS part and transitioned to the real materials when available. If not planned, this would result in a drop in demand that will cause exception messages and priority decisions.

APS tools need to differentiate different demand types, consume forecast based on an inventory goods issue, aggregate the demand types to a total demand, and explode net requirements through all levels of the BOM.

Shared equipment constraints

For clinical programs, one of the critical variables to determine early on is internal manufacturing versus con-tracted manufacturing through a CMO. The more accurate your visibility into the potential network setups for the various nodes of the clinical supply, the more likely you can meet jurisdictional approval dates, and the less often you will need to make last-minute changes when expediting supply to meet the demand. Having a view of constrained equipment, especially in use cases wherein both clinical and commercial teams use the same equipment, will be key.

When clinical does run through the same equipment, data is often difficult to manage. Mature products have a much higher degree of accuracy in the hours-per-unit estimates for both equipment utilization and labor. The dynamic nature of clinical products typically produces a high volatility of efficiency and yields, which can impact the overall supply plan. Buffered risk for this variability can come from multiple batches of the DS level to mini-mize the need for major cleanups (multiple times per month) consistently. At the DP level, efficient scheduling and labor utilization typically favor commercial products, even though demand due dates are what should drive the priority.

APS tools need to assess material availability and constraint utilization simultaneously and schedule the orders for dates that can meet the demand within lead times. The impact of constraints across the network should be assessed. The constraints should be in the form of labor (hours per day) inclusive of multiple shifts or equip-ment (batches per week)

For drug substance, campaign planning is necessary to maximize the capacity utilization of the bioreactors where campaign factors of minimum and maximum batches within cleaning times (major and minor) are built in based on sequences with other materials. The throughput should drive what determines which type of constraint to use.

Clinical and commercial SKUs should drive capacity consumption based on that material's attributes and con-sume the capacity of the production activity at the operation in which the activity is performed. Key metrics in-clude supply volume by clinical/commercial, constraint utilization (planned to actual), and schedule adherence for clinical that is measured to net requirements and not the detailed scheduling process.

When running campaigns from a tactical planning point of view, APS tools should create batches and load con-straints in campaigns (contiguous blocks) to support these campaign requirements:

- **Multiple products/materials within a campaign**: different materials of different batches per campaign, automatically sequenced
- **Multiple constraints**: multiple constraints for one specific production version for one material. For example, manufacturing one drug product involves three major process steps: blending, tableting, and coating, and each of these process steps represents a constraint that should be considered for rough cut capacity planning
- **Batch sequencing criteria**: batches within a campaign to be sequenced using master data parameters. In drug product manufacturing, different materials can be sequenced based on the active ingredient and dosage strength and dosage form. For example, the same active ingredient materials within a group to be checked in the planning horizon and sequenced together accord-ing to a specific time horizon. This helps to schedule major setup/cleaning times only at the beginning and end of a campaign and have only minor setup/cleanup or no setup/cleaning times between batches within a campaign
- **Constrained consumption - sequenced versus parallel**: When there are multiple constraints, such as three constraints for drug manufacturing - one each for blending, tablet-ing, and coating. With parallel consumption, all three constraints would be loaded only when all the constrained/finite load constraints are available. In sequenced consumption, the constraints would be loaded one after the other in a con-tiguous block. Sequenced consumption is the preferred model, particularly when campaigns have longer runs across multiple periods

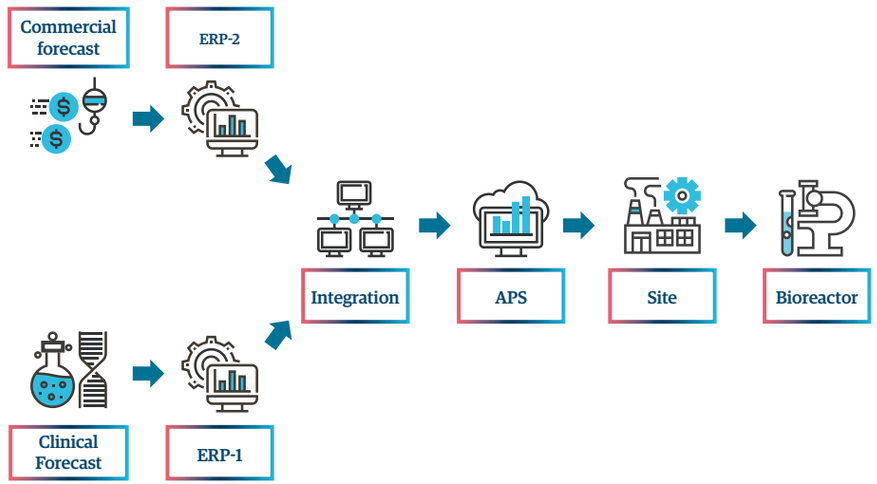


Figure 8. Shared equipment constraints

Regulatory approvals

When a program is approved, the trial is then approved for each individual country. These countries must go through regulatory approvals as well. Examples include the Food and Drug Administration in the United States, the Ministry of Health, Labour, and Welfare in Japan, and the European Medicines Agency in the European Un-ion. Times for review and submission vary for each regulator.

Increasingly, trials will become more multinational as variation drives a more complete answer of efficacy on the worldwide stage faster than single-country trials with less diversity. The complexity of multinational regulatory approvals includes different shelf lives, country of origin requirements, and country-specific approval dates that split the supply on several characteristics and make delivering an accurate supply plan more difficult.

APS tools should have capabilities that allow for supply to match demand based on specific countries' approval dates and split the supply based on lot/batch characteristics to meet the demand based on requirements. This requires a time-phased approach to master data including material/item master, sourcing rules, BOMs, routings, and capacity entities for an effective solve.

Regulatory approvals (also known as jurisdictional rules) are available after the clinical trial approval and in doc-uments such as the clinical trial protocol, certificate of analysis, and analytical specification, which are clinical documents circulated between different teams in the clinical supply chain.

These regulatory approvals typically contain information such as where the clinical trial is conducted. As the study progresses, the number of countries will increase for a more complete view of efficacy on the worldwide stage, and regulatory approvals may involve changes in the property of the drug or even the supply chain net-work of the drug. This requires good feasible tactical planning of clinical supplies.

Mostly, these regulatory approvals are originated/maintained in clinical trial systems that are not integrated with ERP or APS systems, so planners must manually analyze and plan clinical supplies. This is neither timely nor effective.

Regulatory approvals are not only required at the beginning of the study but also in the later stages as the study progresses, more countries and more patients participate, and changes to study characteristics grow in number.

These are some of the common changes that require regulatory approvals:

- Stability-protocol-driven changes in the shelf life of the material/drug:
  - Shell life extension/new shelf life not accepted by some countries participating in the clinical trial protocol
  - As a new shelf-life requirement becomes available from the stability protocol, the change control process (CCP) begins. Planners conduct an impact analysis of the shelf-life change and initiate the regulatory approval process based on the approval where any restrictions are evaluated (for example, a specific study country restriction evaluation) and appropriate restriction actions are applied (for example, shelf-life master data update or creation of new material number), which changes planning behavior
  - For more details, refer to the stability protocols section
  - One supply chain manager stated: "Most of my changes requiring regulatory approvals have to do with expiration date changes"
- Change in the raw material/component of the clinical finished good:
  - Change in drug product or primary pack
- Change in the supply chain network of the clinical finished good:
  - Change in manufacturing site for change in drug product or primary pack (rare)

Common clinical finished good (CFG) supply chain planning network use cases and the impact of jurisdictional restriction rules

Assumption case:

A clinical study involving CFG A (a new drug), currently conducted in Germany, Austria, and Japan. A new shelf-life change (driven by the stability protocol) has been approved only by Japan but not Germany or Austria. CFG A is manufactured (make) with only one production version, which represents a specific primary pack/drug product. CFG A is manufactured at manufacturing site MFG1 and then supplied to the German depot, Austrian depot, and Japanese depot, which are providing clinical supplies to clinical sites such as hospitals.

- **Case one: Creation of new CFG B**. CFG B is created for Japan (in most cases) with new shelf-life data and the same PV as before (because there is no change in component - primary pack/drug product)
  - **Challenge one**: As the time required to set new master data is longer*, the availability of new clinical supplies for CFG B material may be late (due to its own lead time). Planners tend to use existing on-hand inven-tory of CFG A material (batches manufactured before new shelf life from stability protocol) for de-mands on CFG B material. This process is often referred as reservation of stocks or allocations.
    - CFG A (drug product batch A) is usable worldwide
    - Stability protocol extension for drug product batch B (CFG A) means an update of re-striction required because drug product batch B is only approved by Japan
    - New CFG B is created for Japan
    - Deliveries to Japan can be from:
      - New batches of new CFG material number (CFG B) or
      - Existing old CFG batches (CFG A)
      - Japan's forecast for CFG A should be transferred to CFG B
      - Inventory of CFG B and CFG A (only old batches and based on transi-tion scenarios - see below)
    - Deliveries to Germany and Austria can be from:
      - New batches of old CFG material (CFG A)
      - Existing old CFG batches (CFG A)

* The limitation of longer lead times in master data creation and planning can be eradicated by using the APS system for long-term planning using the lifecycle management process

- **Challenge two**: The new shelf-life requirement cannot be maintained for just the Japan depot and use the same ex-isting CFG material network because the shelf-life requirement at CFG MAKE can only be one (for example, after regulatory approval)
- CFG A at German dept, shelf life = 36 months
- CFG A at Austria depot, shelf life = 36 months
- CFG A at Japan depot, shelf life = 48 months (only Japan approved the new shelf life from stability protocol)

Is the CFG A at MFG site shelf life 36 or 48 months? What should the shelf life at the make site be? Should this be the minimum of all shelf-life requirements across all countries or the maximum of all shelf-life requirements across all countries? Either of them would not be accurate across all coun-tries, and this is one of the reasons why a new CFG material is created as CFG B for Japan.

- **Case two: Without the creation of new CFG B.** There may be cases in which CFG A must remain in use due to master data creation and the setup lead time of planning parameters. For example, there may be cases of the same CFG with different country-specific restrictions by country with different regulatory approval dates. For example, Germany has dif-ferent purity requirements, but Japan requires different chromatography tests, and so on

- Transition scenarios for regulatory approval-driven changes:
  - Hard switch: the old drug product cannot be used for CFG after the new drug product has been approved
  - Grace period: the drug product can be used for CFG for an agreed period after the new drug product has been approved
  - Soft switch: the old drug product can be used up first before switching to new drug product
  - Alternative: introducing new PV, after which the old PV needs to be phased out

These examples illustrate how the regulatory approval process creates changes in planning behavior. The key source information required for regulatory approval-driven planning in APS systems includes:

- Restriction details such as restrictions on shelf life, countries, and so forth
- Part and old part linkage. Information on parts that are interconnected for supply and demand alloca-tion as per regulatory approval
- Transition scenario. Information about how the transition should take place between the old and new materials
- Regulatory approval dates like regulatory action status, health authority submission actual, and health authority decision actual, and so forth

The APS should be able to provide automated as well as manual supply and demand allocation using regulatory approvals. There are cases of manual allocation of supply and demand happening in an execution system (for example, a specific process order of a clinical finished good using only one on-hand batch of a PP/DP). An APS should respect these allocations from the execution system but possibly limit changing these allocations in APS planning.

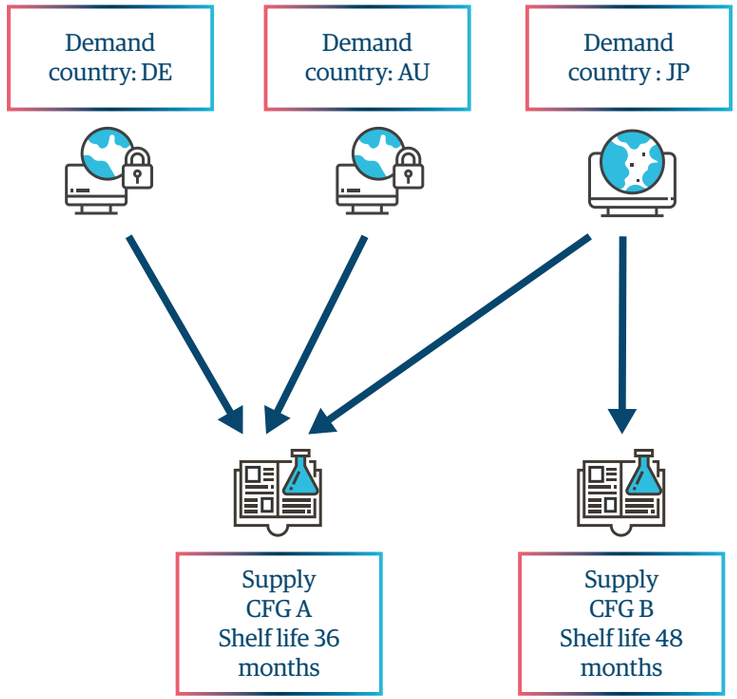


Figure 9. Regulatory approvals

Stability protocols

Planning for changes in expiration dates have a large impact on write-offs and utilization, especially when a SKU has a short shelf life. In the clinical arena, parts start off with a short shelf life because product stability has yet to be scientifically proved, and these studies take time to conduct.

A stability protocol that dictates when the various pull points occur and how the pull point will extend shelf life can drive supply selection and timing of the supply plan. Often, supply in work in process (WIP) as scheduled receipts or on-hand inventory can be reclassified to abide by the updated expiry calculations.

Stability protocol	Pull point date	New shelf life	Recalculate existing inventory/WIP
Drug A - pull point 1	01-Jun-2022	18 months	Yes
Drug A - pull point 2	01-Sep-2022	24 months	Yes
Drug A - pull point 3	01-Mar-2023	30 months	No
Drug A - pull point 4	01-Sep- 2023	36 months	No
Drug A - pull point 5	01-Sep- 2024	42 months	No

In supply planning using a stability protocol, APS tools should be able to match the various pull points to the correct number of days to expire to minimize waste. Planning should be executed on a 'first expiry first out' (FEFO) basis, with the opportunity for planners to either include existing inventory under the original shelf life or the new shelf life. Future planning should allow for different shelf-life data based on the planned manufacturing dates.

The specific capabilities required would allow entry of the complete stability plan into the APS tool. The data would include the various dates on when and to what the shelf life can extend. In this way, planning can incorporate all the planned expiration date changes and match supply to demand to the changes considered. This alignment can then further scale manufacturing to the appopriate lot sizes based on the coverage that each lot will provide.

Additionally, any inventory quantity that was originally expected to be expired could be recovered and pegged to demand further out.

Finally, these planning results should be tied to execution in the ERP system to link planning and execution as a continuous flow, where the ERP system is maintaining the current shelf life and execution elements, and the APS houses the future shelf life and planning elements.

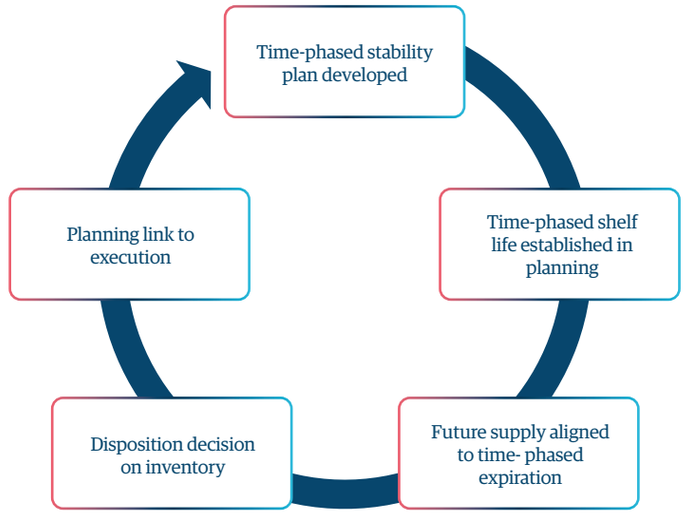


Figure 10. Stability protocols

As the new shelf-life requirement is available from the stability protocol, the change control process (CCP) be-gins. Planners conduct an impact analysis of the shelf-life change and initiate the regulatory approval process based on the approval. Any restrictions are evaluated (for example, a specific study country restriction evalua-tion) and appropriate restriction actions are applied (for example, shelf-life master data updates or the creation of a new material number, and so forth), which changes planning behavior.

The table below shows sample demand and supply datasets along with expiry requirements and how APS can use the stability protocol in replenishment planning. The left-hand side of the table depicts planning behavior without a stability protocol, while the right-hand side depicts planning behavior with a stability protocol.

The planning result is on the same day (October 1, 2020) for the same material, and the current shelf life of the material is 12 months. As per the stability protocol, the first pull point is June 1, 2022, and as on that date, the shelf life is extended to 18 months.

In the planning without stability protocol, the expiring on-hand batch quantity is not utilized for demand 2 and an excess new planned supply is created. Whereas in the planning with a stability protocol, the expiring batch is replanned and made available by the upcoming pull point (June 1, 2022) with a new extended expiry date (the shelf life is 18 months) which can satisfy demand 2 without the need to create excess new planned supply.

The number of new planned orders generated with a stability protocol replanning are reduced compared to the number of new planned orders generated in planning without it. Stability protocol-based replanning helps to re-duce waste by limiting the number of planned orders generated.

Without Re-planning with stability protocol			**With Re-planning with stability protocol**		
Today-Oct 1, 2020			**Today-Oct 1, 2020**		
	Date	Qty		Date	Qty
Demand 1			**Demand 1**		
Total quantity		80	Total quantity		80
Due date (delivery date)	Nov 2020		Due date (delivery date)	Nov 2020	
Min shelf life requirement date	Feb 2021		Min shelf life requirement date	Feb 2021	
On-hand batch 1 (Id: 123)			**On-hand batch 1 (Id: 123)**		
Due date (release date)	Oct 2020		Due date (release date)	Oct 2020	
Current expiry date (due date + shelf life (12 months))	Sept 2021		Current expiry date (due date + shelf life (12 months))	Sept 2021	
Total quantity		100	Total quantity		100
On hand quantity consumed by demand (before sept. 2021)		80	On hand quantity consumed by demand (before sept. 2021)		80
Expiring on hand quantity (by September 2021)	Sept 21	20	Expiring on hand quantity (by September 2021)	Sept 21	0
			Replanned On-hand batch 1 (ID: 123), 6 month extention		
			Replanned due date (release date) as per stability protocol pull points	June 22	
			Replanned expiry date (Replanned due date + Shelf life (18 months))	Dec 2022	
			Total quantity		20
			On hand quantity consumed by demand (before Dec 2022)	Dec 2022	20
			Expiring on hand quantity (by Feb 2022)	Feb 2022	0
Demand 2			**Demand 2**		
Total quantity		20	Total quantity		20
Due date (Delivery date)	Nov 2021		Due date (Delivery date)	Nov 2021	
Min shelf life requirement date	Feb 2022		Min shelf life requirement date	Feb 2022	
Planned order quantity - due date* November 2021		**20**	**Planned order quantity - due date* November 2021**		**0**

Comparator management

Pharmaceutical companies spend millions of dollars every year determining and sourcing comparators for clini-cal trials. Comparators can be active, such as a commercially available drug, or inactive, where it is the same exact recipe excluding the active ingredient. Regardless of whether it is an inactive placebo, a commercially available control, or an internally manufactured investigational drug, sourcing rules require it to be managed in the same way as the test groups. Comparators should follow the same processes as the test groups.

As trials become more geographically dispersed, the logistics of having the comparators imported to different countries will add complexity to managing the trial. Planning processes require regulatory-approved supply chains, appropriate and timely demand signals to match enrollment plans, and logistics considerations such as shipping conditions and import/export licenses. Comparators need to consider the standard challenges of com-mercial products with expiry, changing approval dates for regulatory bodies, country of origin requirements, and minimum remaining shelf life to be considered usable for a trial.

Ultimately, the goal is to provide the treatment on the right date at the clinic per the enrollment plan in order to obtain valid test results for the study and maximize the benefit to the patient for having elected to enroll in the study.

For APS tools to support comparator management, the source selection needs to be scalable and integrated into the study. They must act as a data management system to create the sourcing rules for the comparator. For some study types (for example, double-blinded studies), the comparator must be indistinguishable from the test groups and be replenished to the clinical sites in the same manner, regardless of demand.

4PL collaboration

The nature of external relationships has evolved in clinical trial management to where 4PLs are aligned as stra-tegic partners and integrated into the clinical supply chain. Traditional 3PLs are more transactional, warehousing and shipping the trial materials to the clinic site but not co-planning or taking responsibility for the success of the trial. The graph below summarizes 3PL and 4PL relationships and the degree of process involvement that each should have.

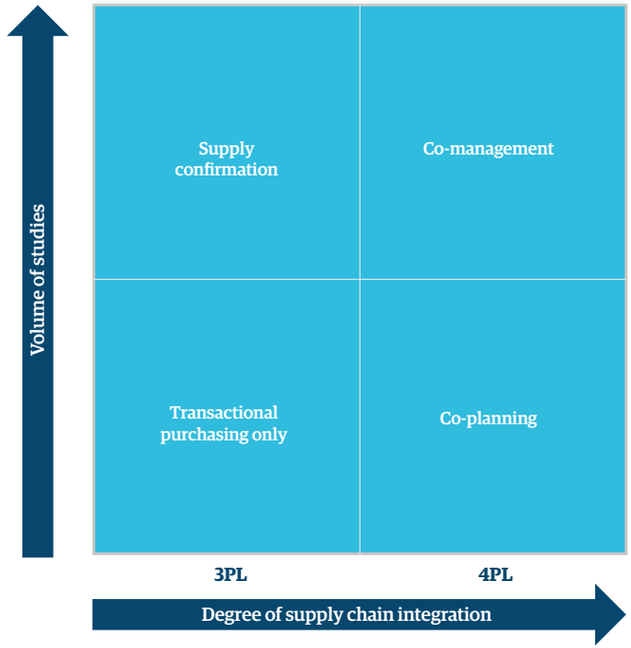


Figure 11. Supplier collaboration model for clinical planning

For trials with limited supply chain integration and low volumes of samples or trials, the partnership should be transactional only. A purchase order should be issued with delivery dates and quantities to clinics with all the management and changes owned by the pharmaceutical clinical organization. If a change in approval dates or enrollment patterns changes demand, the updates will be made and communicated to the 3PL. Likewise, if there is a supply challenge with expiry or approval, the changes to batch selection would be dictated by the program to the vendor who executes what the clinical program as contracted.

For high-volume trials with limited supply chain integration, an additional step should be considered in planning. Changes in supply and demand are typically emailed back and forth, and the execution of the 3PL is based on a time-phased review. The review provides the ability to confirm a statement of supply and appropriate inventory levels at the 3PL. Any risk mitigation strategies such as buffered stock could be agreed to and sent to the 3PL.

For low-volume trials that have a high degree of supply chain integration, co-planning should take place. The 4PL's network should be planned as if it is an internal node in the pharma company. Daily integration of supply, demand, and inventory changes should immediately highlight impacts on the trial, with the necessary expedites to ensure that the enrollment periods for patients will be met. Buffered stock can be at both nodes of the supply chain, and complexities such as double-blinded studies would carry enough coverage to ensure that all patients have access to the correctly blinded control substance through the risk-based coverage.

For trials with high volumes and a high degree of supply chain interaction, the pharma company relies on the 4PL as an extension of the organization. In this co-management model, every aspect of delivery to the clinics is the 4PL's responsibility, catering to the oversight of the clinical program. In this case, real-time data should be available to both organizations, and decisions are a shared responsibility based on integrated systems and co-responsibilities.

APS capabilities should be able differentiate and model 3PLs and 4 PLs differently based on the partner/vendor's quadrant. Increasing complexity requires more capabilities:

- Enable shared net requirements
- Allow for a supply confirmation from the vendor/partner
- Model as part of the extended BOM
- Allow for access to shared data
- Manage the execution elements as actuals in a shared environment
- Participate in supply reviews as part of a clinical S&OP session

Customized KPIs and reporting

Forecast-related KPIs

Demand stability

To monitor the stability of regulatory approval dates (without historical demand actuals being relevant)

- Forecast volume and timing delta difference between last forecast period and the current forecast period
  - Between different materials, handles cases of transition between planning material with long-term forecast versus actual material with clinical forecasts, which provides a ramping picture to adjust forecast discrep-ancies

- Approval dates can shift by country. Monitoring this and driving this as demand instability into the CS&OP process can maximize supply chain responsiveness between regulatory, planning, and executive level re-sources

Forecast accuracy

In general, to calculate and monitor overall forecast accuracy by comparison with historical demand actuals (for example deliveries)

- As the historical demand actual (HDA) records/shipment cover different categories of forecasts (for example, a de-livery record can cover clinical forecast actual enrolled patients as well as clinical forecast planned patients for a specific clinical site) as well as multiple periods of forecasts (for example, a delivery record can cover multiple months of clinical forecasts). We have a custom logic for forecast accuracy calculation.
  - Source data: actual: historical demand actuals (loaded from ERP) and historical forecasts (to be archived in the APS)
  - Calculation: historical demand actuals versus historical forecast
  - Actual: cumulative sum of actuals starting from first shipment/actual record until the latest (up to today) because one shipment can cover multiple periods of future forecasts when that shipment was created
  - Historical forecast: sum of forecast values based on chosen lag (three options/variables) until today plus however many months into the future with the ability to choose three lag points
  - Level: the above calculation needs to be below individual levels. The material study at the part level is from SAP:
    - Material_Study
    - Material_Depot (Site)
    - Material_Depot_Study_Country
    - Study_Country
  - Parts and forecast categories selection criteria: clinical forecasts can be for different categories like clinical actual enrolled patients, clinical planned patients, and so forth

Inventory-related KPIs

Inventory quality ratio

Inventory quality ratio (IQR) is a simple but exhaustive measure to verify inventory health. By comparing batches that have a good receipt date (no later than, for example, nine months) against total stock available, slow- or non-performing inventory can be easily identified. This shows where action is required to review current safety stock levels and reduce inventory. The APS tool can present this as a pie chart or a detailed table view to identify materials that are causing deviations because the IQR graph can be viewed at different levels of aggregation (at the study or trial level, for example).

IQR is represented by this simple equation:

- $$\text{IQR} = \frac{\text{Good inventory}}{\text{Total inventory}}$$

- Good Inventory can be considered as the number of non-expired batches with a good receipt date no later than nine months before the current month
- For some material types such as drug substance, the good receipt date might be replaced with the last movement date

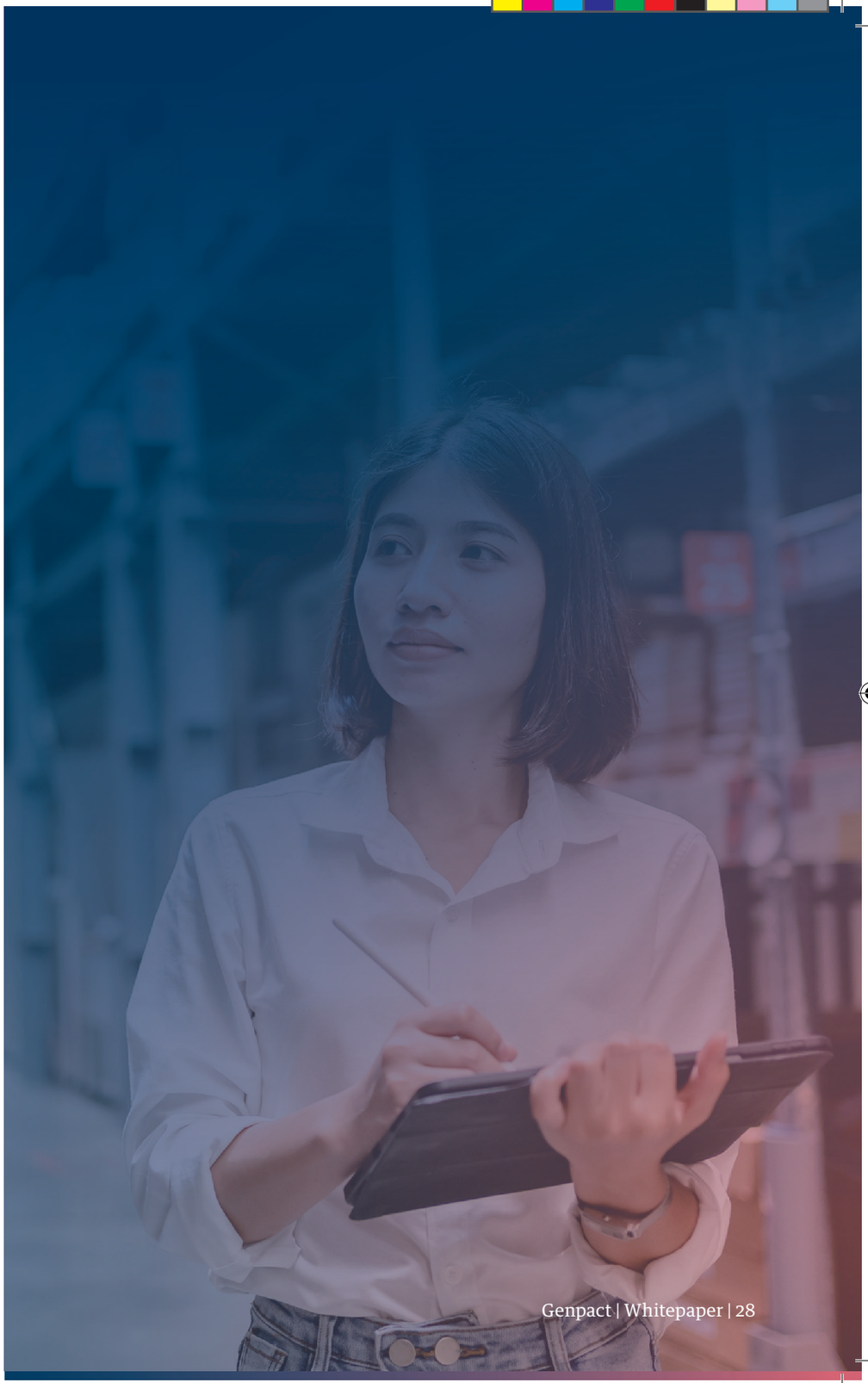
Supply-related KPIs

On time, in full (OTIF)

OTIF is a supply chain effectiveness measure that feeds into a CS&OP process supply review. This KPI considers orders received at the due date of a demand and in the quantity expected by the order. The denominator should include orders based on the net requirement calculation. By design, the APS tool will be set up to fulfill orders only in a full quantity so all orders that are available according to the expected due date should be considered as in full as well. Analytics should postpone the material available date in case the quantity is either in hand, upcoming for production, meant for different locations, or not enough to fully accommodate demand.

Following this logic, the supply available date against the demand due date is suitable for this measure's calculation. Metrics should be considered two ways: as both a projected and historical data analysis. This gives the full spectrum of past performance and, according to the current supply plan, all expectations for the coming months, considering historical data corrective actions can be taken, such as lead time recalculation or deeper constraint analysis. Projection can help to point out the periods with expected challenges, and a brought analysis may lead to supply plan changes to prevent upfront risks.

- OTIF is represented by the equation:
  - $$\text{OTIF} = \frac{\text{Number of orders received on time and in full}}{\text{Total number of orders based on net requirements}}$$
- Key data points required for the calculation:
  - Historical OTIF: historical demand actuals and supply demand actuals including due dates, available dates, requested quantities, and received quantities
  - Projected OTIF: demand due dates and supply projected available dates reference information



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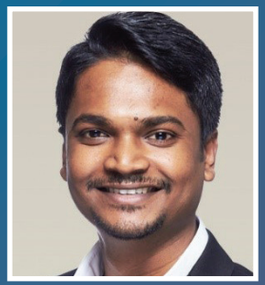
- Architected clinical and commercial planning integration for pharma-specific companies



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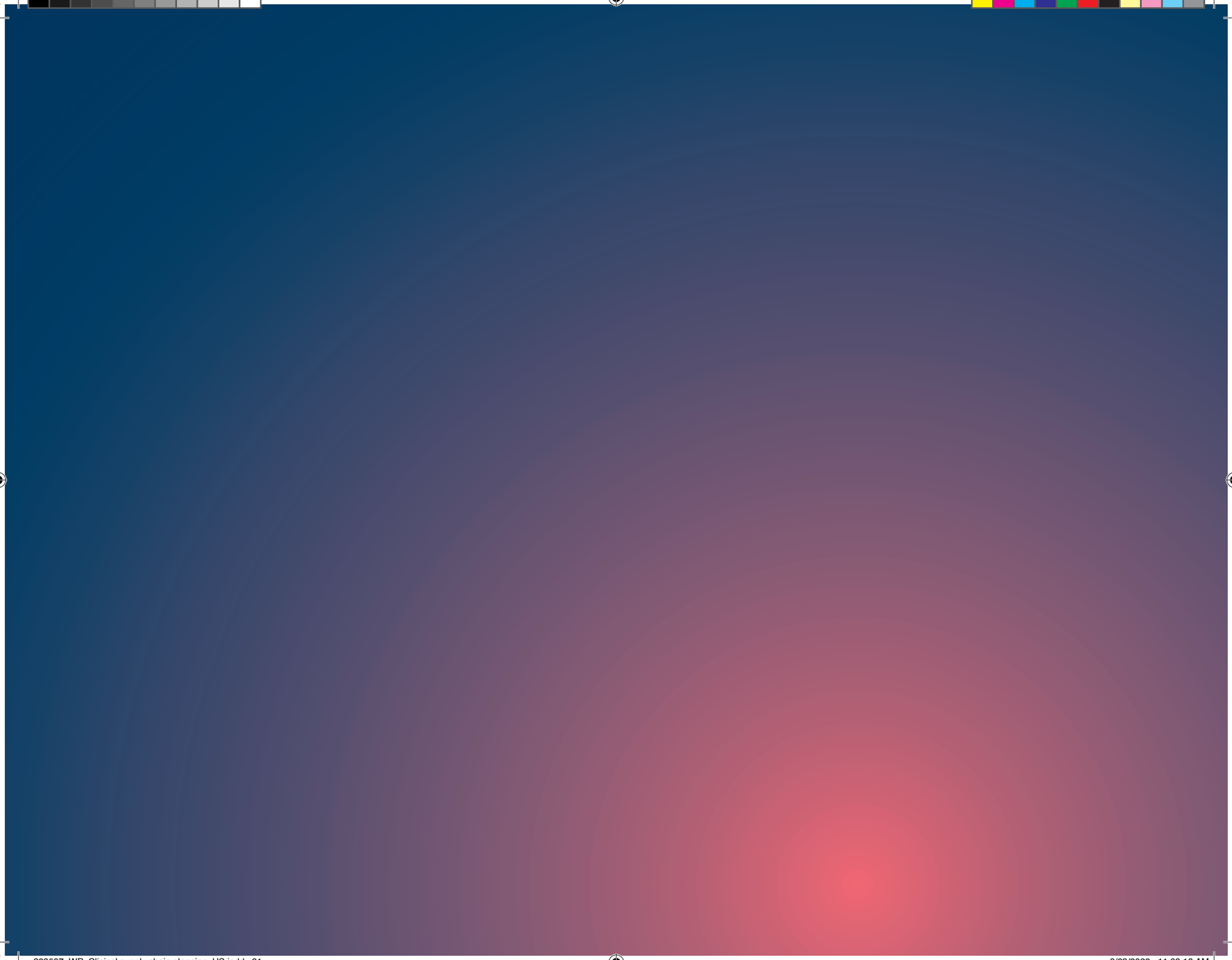

About Genpact

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