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BRINGING PRECISION MEDICINE TO MARKET

DIVERSE THERAPIES CREATING COMPLEXITY AND DIGITAL INNOVATIONS DRIVING MODERNIZATION

CONTENTS

INTRODUCTION

We live in an amazing time when it comes to biopharmaceutical drug discovery and development. The FDA has approved innovative medicines with differing approaches, platforms, technologies, and modalities. As we leverage new technologies, our strategies for drug discovery are leading to therapeutic diversity which is rapidly becoming a complicated landscape for manufacturing teams.

With modalities as diverse as small molecules, monoclonal antibodies, CAR-T cell therapies, RNA-based therapies, and personalized vaccines and medicines for patients, the portfolio strategy for Executive leadership and R&D teams has led to increasing complexity for Chief Manufacturing Officers and their teams.

Figure 1 shows a few recent examples of these product launches – almost all are first-in-class therapies solving real health problems with diverse modalities.

Figure 1. Recent FDA approvals have created complexity for manufacturing teams.

As these companies are acquired, leadership is discovering that the traditional paradigm of acquiring, integrating, and closing the acquired organization is no longer feasible because they cannot easily replicate the expertise and manufacturing capabilities.

CAR-T Cell Therapies

One of the most exciting new treatments coming to market is CAR-T cell therapy. This treatment utilizes reengineered T-cells tagged with a chimeric antigen receptor (CAR) to target patient's cancer cells. As the Figure 2 describes, there are two methods of CAR-T cell therapy, Allogenic and Autogenic.

Autogenic therapy involves point to point infusion, taking cells from a sick patient, formulating them appropriately, then infusing back into the same patient. As you can imagine this requires supply chain intricacies to ensure that the one-to-one infusion is maintained. In addition, due to the long lead-time between collection and treatment as well as severity of disease progression in patients receiving CAR-T therapy, patients have passed before receiving the reinfusion.

Allogenic therapy does not rely on point-to-point treatment but instead collects T-cells from healthy donors. Once cells are transduced with the viral vector (CAR) they can be inventoried for off the shelf infusion for many patients. While this simplifies the supply chain tracking and reduces the lead-time for treating a patient, Allogenic therapies come with their own complexities. For example, identification of suitable donors that qualify for cell collection is incredibly difficult. Donors must not have been infected with a variety of different illnesses to ensure a consistent T-Cell is collected. In addition, there is high variation between donor cell yield during proliferation that is not yet fully understood.

Figure 2. CAR-T overview.

CAR-T Cell Therapies

In the eco system of novel drug discovery and launch, competition not only exists between companies racing to be first to market, but within the third party supplier arena as well.

Many of the raw materials and production facilities required for CAR-T therapy manufacturing stem from a small group of key suppliers (Lonza, Lentigen, WuXi, etc.) As the market continues to grow, these suppliers are forced to either expand their production capacities or selectively choose which customers will receive their goods/services. Of course, their demand is much smaller than that of a later stage company and without strategically partnering with big pharma companies that have “supplier pull” they may be considered second priority to suppliers. This leaves smaller biotech companies at a potential disadvantage. Figure 3 shows key suppliers across the supply chain.

Figure 3. Prominent suppliers in the CAR-T space.

Viral Vector

Lentigen · novasep (passion & smart processes) · Vigene Biosciences (Excellence in Gene Delivery) · creative biogene (BIOTECHNOLOGY)

Manufacturing

药明康德 WuXi AppTec · Lonza

Media

Lonza · MACS Miltenyi Biotec · cellectis (EDITING LIFE) · SIGMA-ALDRICH

CAR-T Cell Therapies

While it is potentially possible to use multiple suppliers, variation in different supplier raw materials (and even production practices) raises additional regulatory questions that could impact approval and potentially require comparability studies to evaluate purity, functionality, and efficacy.

Mitigations for these risks include building in house production capacity, developing strategic relationships with suppliers, appropriately auditing third party vendors, and establishing robust supply agreements (Figure 4). Biotech companies must risk mitigate as they move towards pivotal and commercialization.

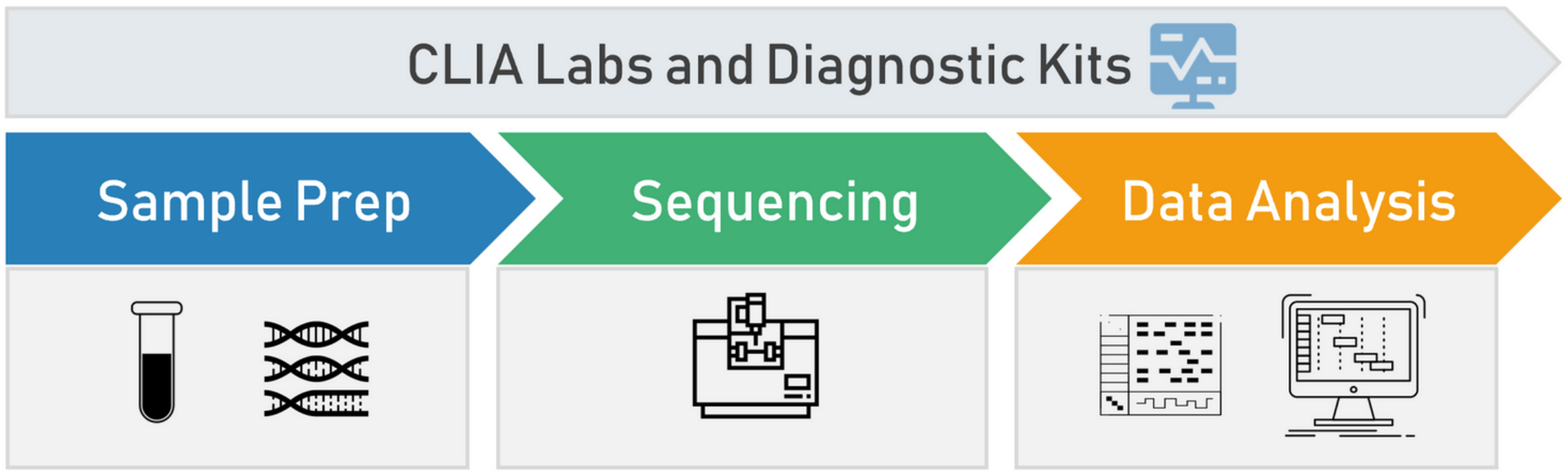
Figure 4. Supplier management strategies.

As the space continues to grow, invariably more suppliers and novel technologies will emerge. Companies of all sizes must keep a finger on the pulse of the supplier market, continuously vetting emerging raw materials, equipment, and manufacturers while balancing this with production longevity.

Next Generation Sequencing (NGS) and Application to Personalized Vaccines and Therapeutics

Sequencing technologies will further integrate into the manufacturing environment as we develop personalized medicines and vaccines for patients. With Sequencing technologies, this is fast becoming a reality. But these technologies require a clinical laboratory (CLIA - Figure 5) to do the sequencing, for the sequences to be sent to the manufacturing facility, and for that manufacturing facility to produce the personalized therapeutic for a patient.

Figure 5. Next generation sequencing's end-to-end solutions.



Today

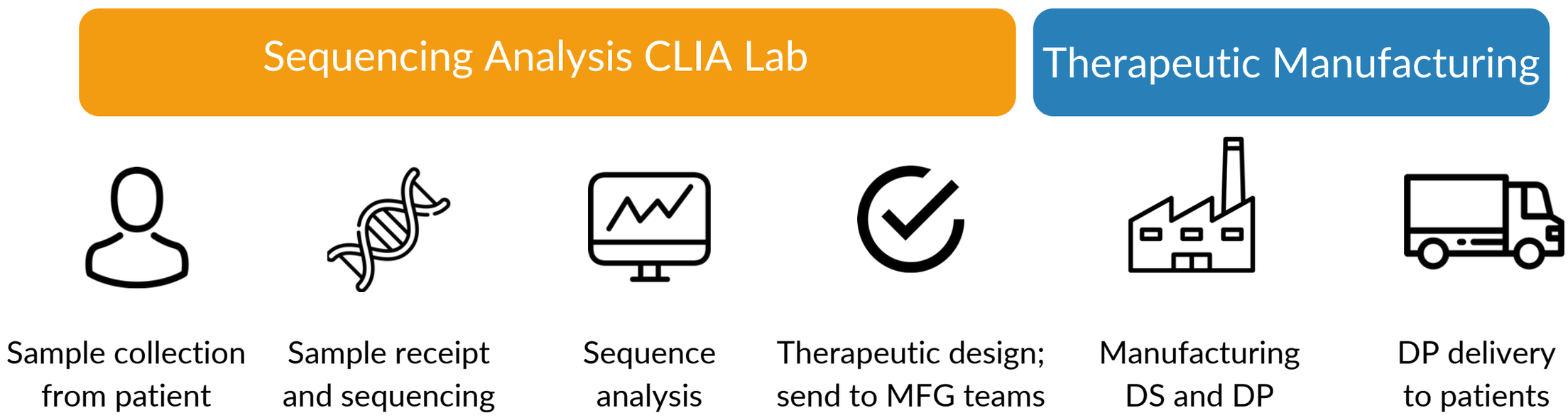
Sequencing businesses focus on end-to-end workflow solutions that allow informed decision-making by Doctors and Patients.

Tomorrow

Sequencing businesses will support pharmaceutical and biotech companies that want to produce customized vaccines and therapies for Patients.

For the Chief Manufacturing Officer and their teams, this means integrating production processes with sequencing technologies along with CLIA labs (Figure 6) to analyze and provide instructions for customized therapies to the manufacturing plant's teams.

Figure 6. Operations for personalized therapies involving NGS technologies.



EVERY PATIENT IS A "BATCH"

Personalized Therapies Require New Systems

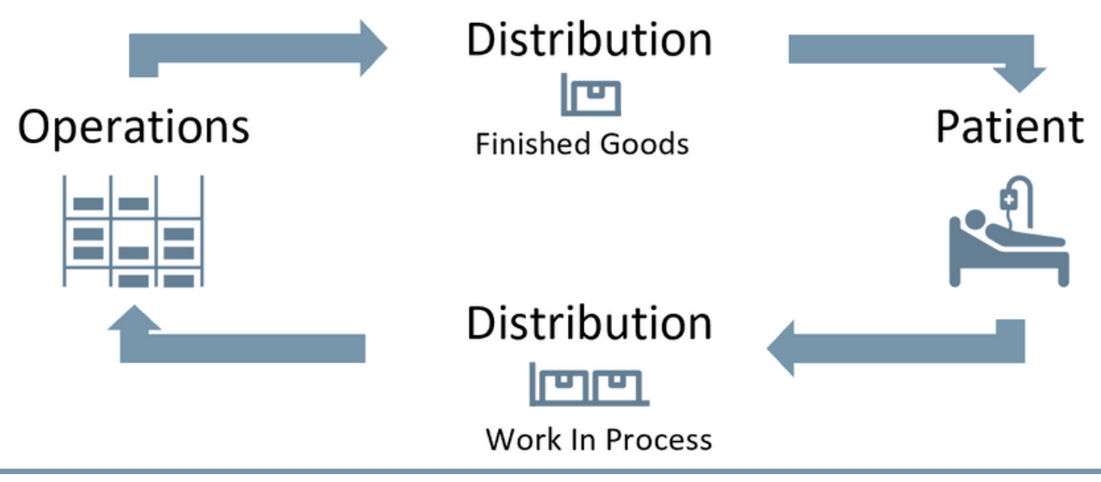
The need to treat each patient as a unique scheduling, setup, processing and fulfillment challenge is requiring innovative supply chain concepts to manage chain of custody, keep bottleneck operations utilization rates high, while delivering effective and safe treatments. Currently these new challenges make treatments costly and provide significant opportunity to innovate and reduce costs in delivering personalized treatments.

Figure 7. Conventional Approach: 1 API = All Patients

Conventional therapies are **make-to-stock** and "one directional" minimizing the patients role in operations

In the more conventional treatments, target indications are addressed with specific molecules keeping the technical operations separated from the patient in meaningful ways (Figure 7) and are typically focused on finished goods inventory levels. Today's "every patient is a batch" more intimately links treatments with patients and as such requires new controls on work in process inventories and finished goods (Figure 8).

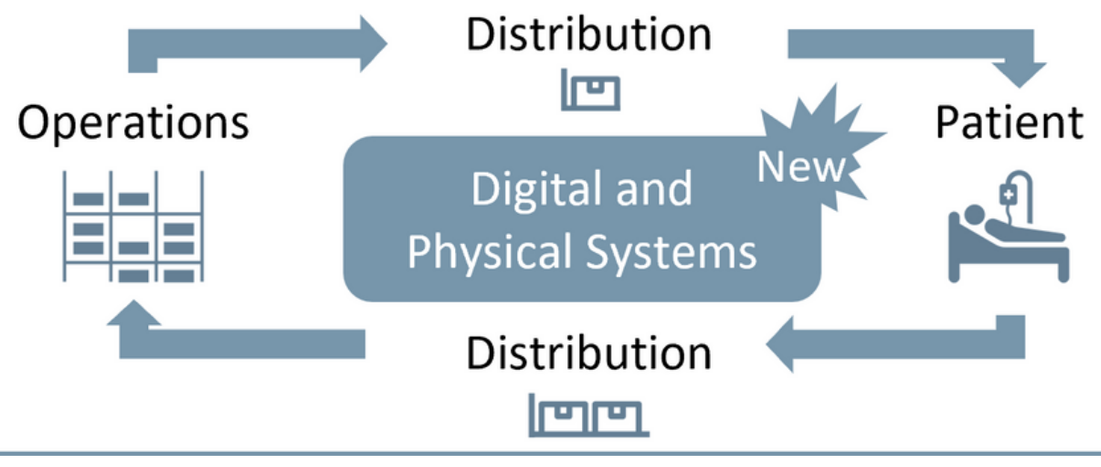
Figure 8. Personalized Therapies: 1 Batch = 1 Patient



Personalized therapies must be carefully controlled to assure that the **unique treatment** gets scheduled, produced and delivered to the **right patient**

These new controls often take the form of new digital and physical systems (Figure 9). Because the patient is linked to tech-ops in this environment, the digital assets (software technology to schedule, track, and administer medicines) may also be a required part of the BLA Filing.

Figure 9. New Digital and Physical Systems



New digital and physical control systems include:

- Patient and doctor portals for scheduling
- Inventory chain of custody
- Sales and billing systems

EVERY PATIENT IS A "BATCH"

Personalized Therapies Require New Systems

Just as with make-to stock production, the need to keep inventory levels low, meet due date requirements, and efficiently operate the facility are paramount to a company's success and competitiveness in personalized therapies.

WHAT IS NEEDED TO SCALE FOR SUCCESS?

Partnerships, Acquisitions or Unicorn

There are different strategies and business models a company can use to have R&D and Commercial success. Those pathways differ for each company and there are many options. In general, companies that raise capital smartly, invest wisely, and strike key partnerships with great science are the most successful.

Companies have followed different strategies, and history shows us that certain paths are less risky for longer-term success for the startup organization. Strategies have included Partnership, Acquisition, and Unicorn.

There are many examples of companies (Figure 10) with a primary strategy of raising money, sharing risks and costs, and having expertise to development and launch a successful first drug candidate through a "Partnership Strategy."

Figure 10. Examples of successful partnership strategies… with an acquisition finale.

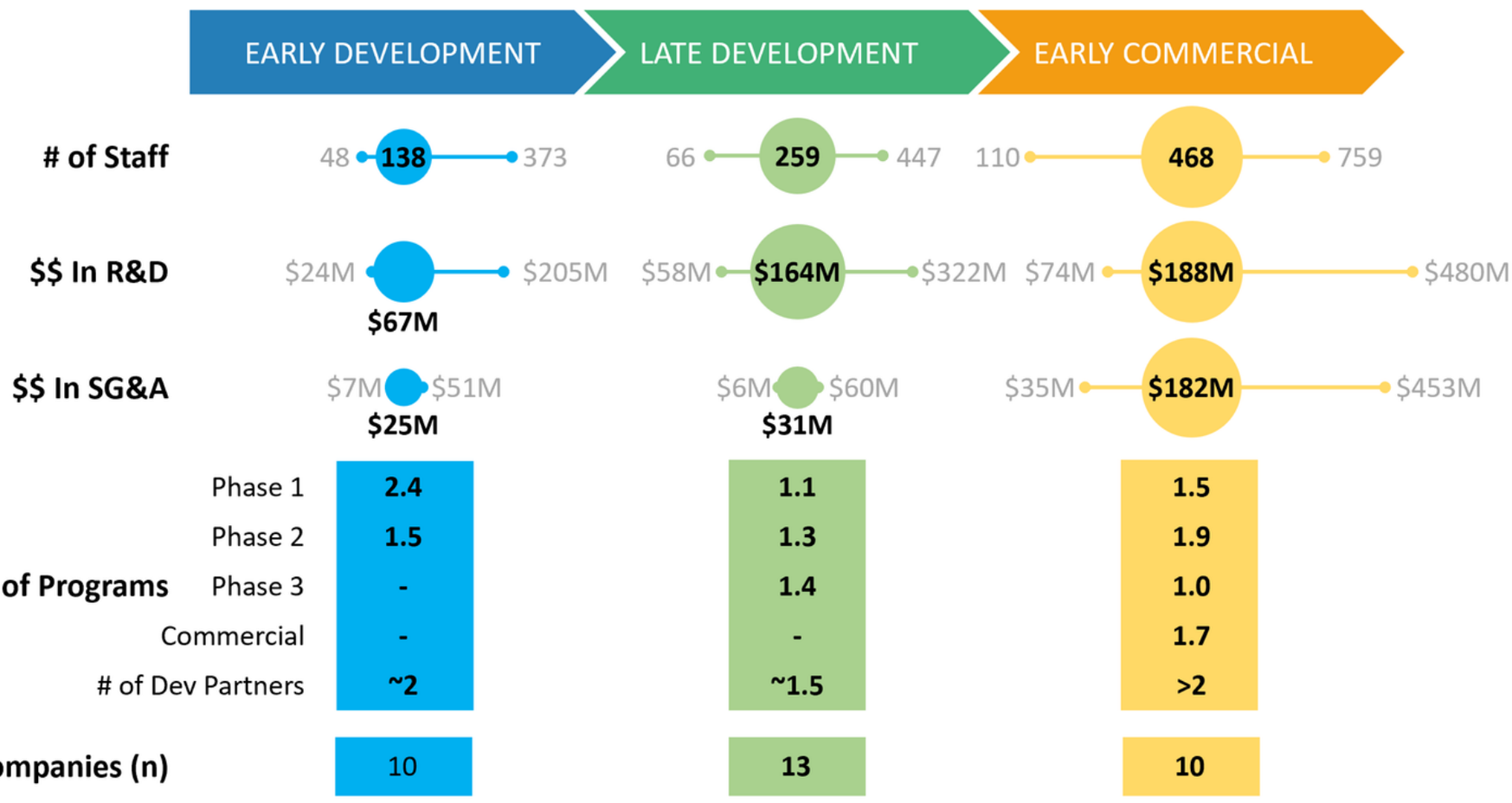
Partnerships, Acquisitions or Unicorn

There are far fewer examples of “Unicorn Strategy” companies (or as close as you can be) prior to launch of their products (Figure 11).

Figure 11. Examples of successful unicorns and their products.

Each company must assess their assets, the pros and cons of each strategy, and the best path forward for their company and patients. In the end, any company’s strategy must translate into shareholder value. The investments they make and choose along the way can have a favorable or negative impact on their business. Scimitar conducted a benchmark on companies by stage of development comparing investments in staff size, R&D, SG&A, and in their programs (figure 12).

Figure 12. Comparing investment strategies across the development lifecycle.



Successful companies had the following characteristics:

Staff: Managed transitions and hired the right people at the right time
Portfolio Balance: Had one Phase 3 program, one Phase 2 program
Partnerships: Had one or two large pharma development partners to support development costs and diversify risk.

CONCLUSIONS

Diversity Management

As with the emergence of MAbs 30+ years ago, companies had to determine how best to manage small molecule and biologics. Organizations created central teams with capabilities such as Quality Assurance, Demand Planning, and CMC Regulatory to manage a portfolio of products with differing modalities. In other cases, companies deployed highly specialized resources to ensure the right technical capabilities such as MSAT, Supply Chain, and Quality Control. The solution at each company will be different, and will depend on their unique circumstances, with the common goal of providing patients with the highest Quality while managing cost and budget implications.

Network Strategy: To Build, Partner, or Both

This will all depend on the companies stage of development and commercialization. There is tremendous competition for resources – in many cases CAR-T Cell companies and gene therapy companies are competing for several of the same contract manufacturing organizations (CMOs), suppliers, and contract testing labs (CTLs). Supplier consolidation has created an environment of supplier power, and weaker positions for the biopharmaceutical manufacturing teams to negotiate effectively potentially leading to higher costs in the future. As a result, a strategy that solely uses CMOs will not be sustainable in the long-term, and companies will need to evaluate in-house manufacturing capabilities.

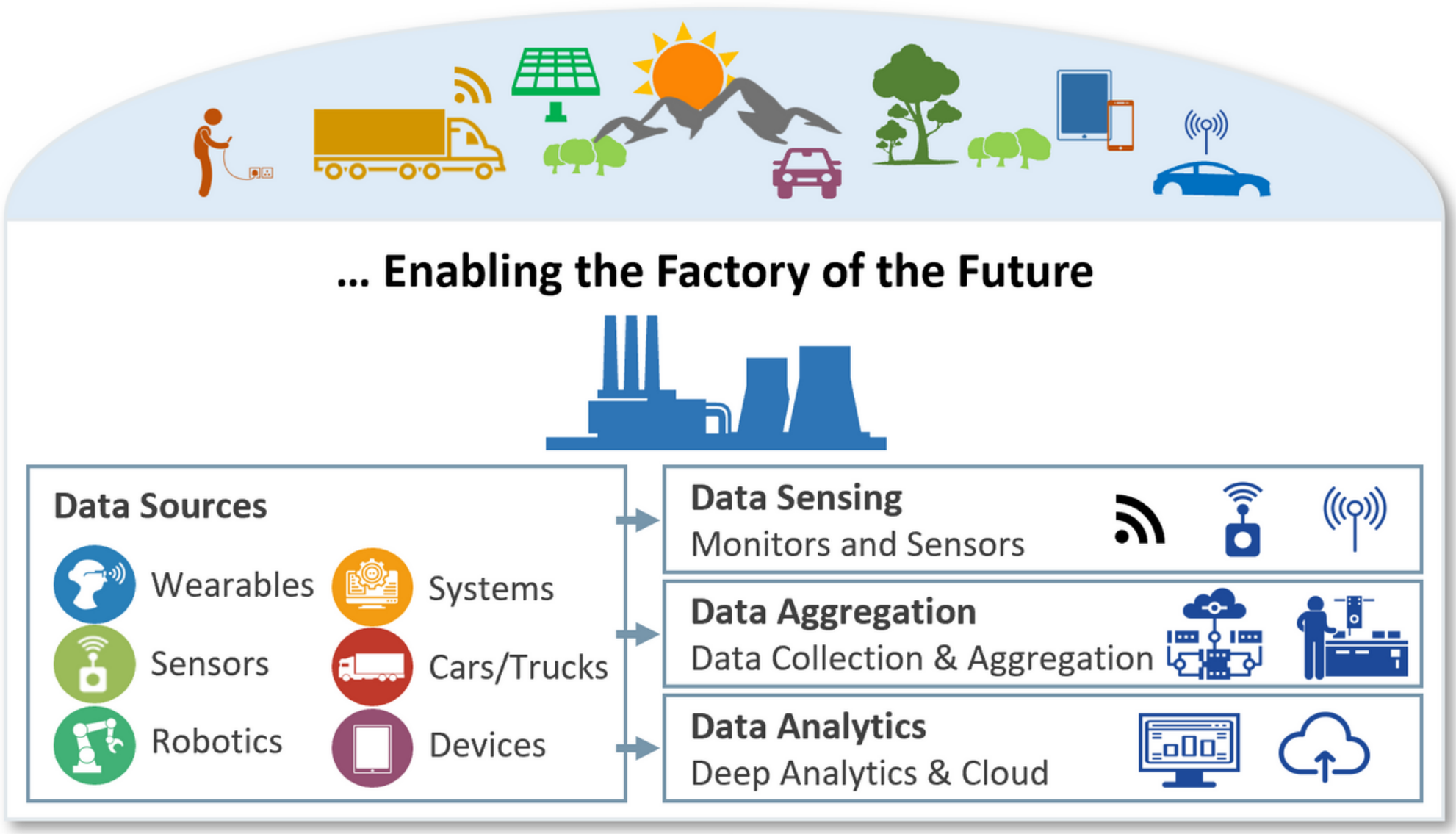
Modernization of Our Manufacturing Plants

We can already see that traditional manufacturing plants with stainless steel fermenters are adapting their capabilities to single-use production processes in an attempt to drive down costs, reduce upfront capital investment and depreciation costs, and allow for facilities with multi-product manufacturing capability.

Modernization of Our Manufacturing Plants

Digital technologies will further integrate into our facilities. Digital technologies will be used to help our teams. We have seen technologies such as Google glasses, digital supply chains, visual factory boards, etc.

Figure 13. Modern innovations.

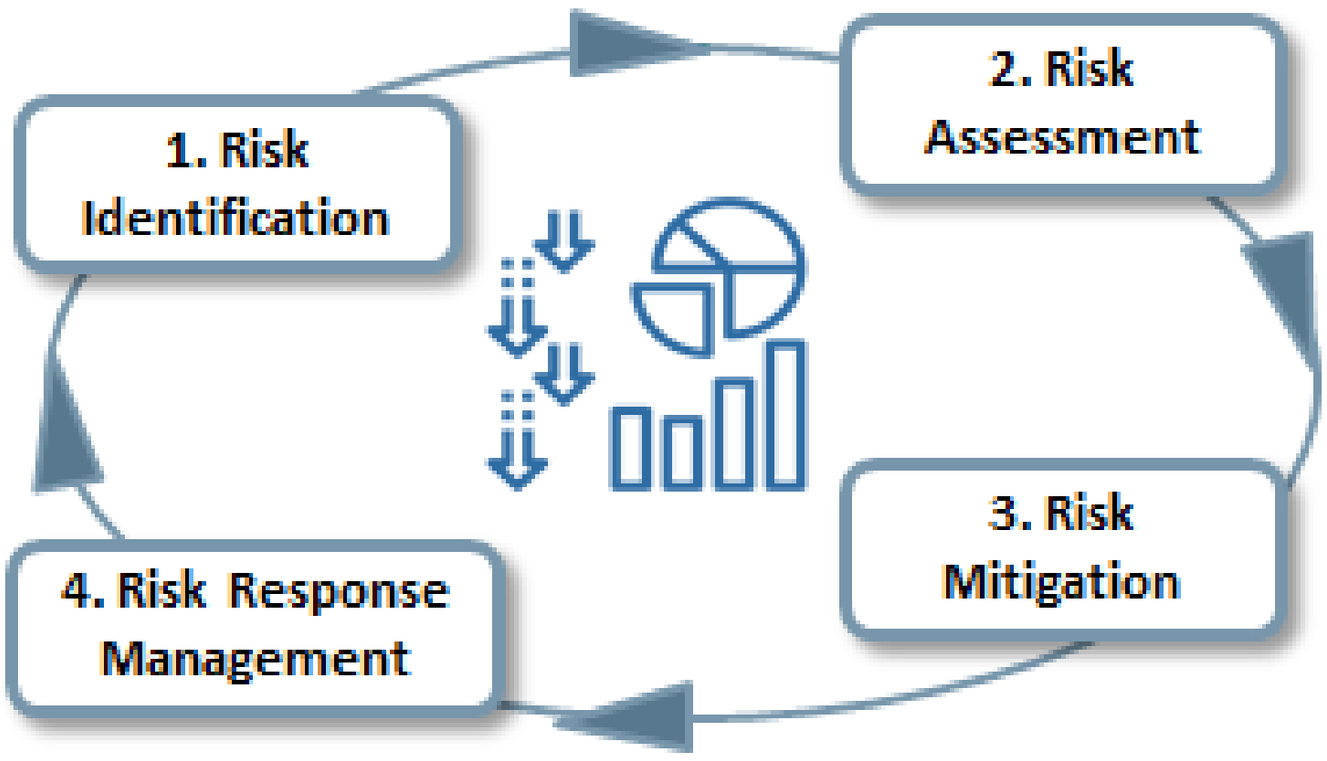


Scimitar is positioned to help Manufacturing teams support their corporate R&D and Licensing strategies to diversify their portfolios. We can support you and your teams in a variety of ways including:

- Integration of Newly Acquired Technologies
- Manufacturing Strategy and Network
- Portfolio Strategy and Placing Bets
- Digital Technology Roadmap and Realization
- Strategic Workforce Planning and Complexity Management
- Supply Chain Risk Assessment

Our experiences in Personalized Vaccines, Sequencing Technologies, and CAR-T Cell therapies is unique for any consulting firm. We can partner together to help enable your near and long-term company success, and support the organization’s efforts to help patients live better lives.

CASE STUDY 1



OVERVIEW

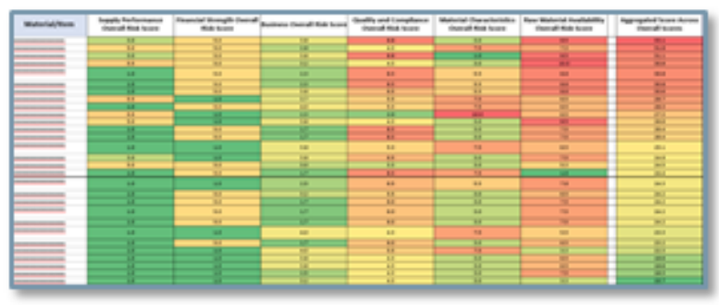
A $3.5B CAR-T Cell Therapy Startup Experiencing Rapid Growth and Required a Supply Chain Assessment

ACTION

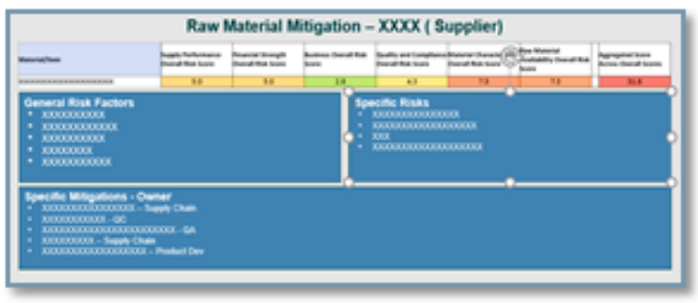
Partnering with the client, the Scimitar Inc. team:

- Initiated a cross-functional core team consisting of members from supply chain, product development, and QC
- Held several working team sessions to assess risk across the organization
- Assessed both quantitative and qualitative risks, translating tribal knowledge into measurable metrics

Heatmap of Raw Material Risks



Risk Mitigation Identification



RESULTS

The Scimitar Inc. team worked collaboratively across the organization to:
Build an end-to-end supply chain materials map including key equipment and testing

- Developed a systematic and replicable process for evaluating risk
- Executed a cross departmental evaluation of all key raw materials
- Developed mitigation plans, priority, and business cases for raw material specific risks and for risks across the supply chain

Mitigation Prioritization

CASE STUDY 2

- Diverse cultures working within rapidly changing operational environment
- Several IT systems integrated with the Cell Therapy offering

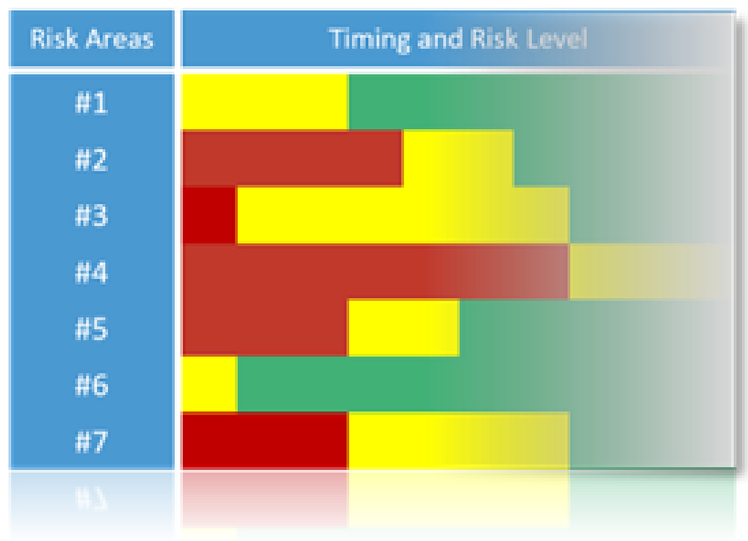
OVERVIEW

Newly acquired CAR-T Cell Therapy Company established growth targets required aggressive scaling of lab, infrastructure, and operating systems.

ACTION

Assessment and IT Integration Planning for support of growth targets and reduction of complexity of key operating systems.

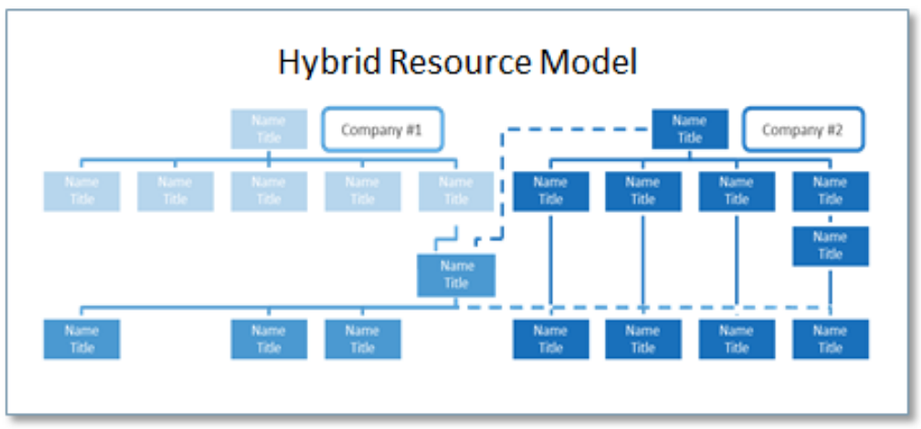
Improvements



RESULTS

Scimitar Inc. delivered assessment and transition risk mitigation plans including:

- Approved Hybrid Resource Model
- Site IT Leadership Transition Plans
- Key system risk areas and mitigations plans
- Mitigation levels and timing



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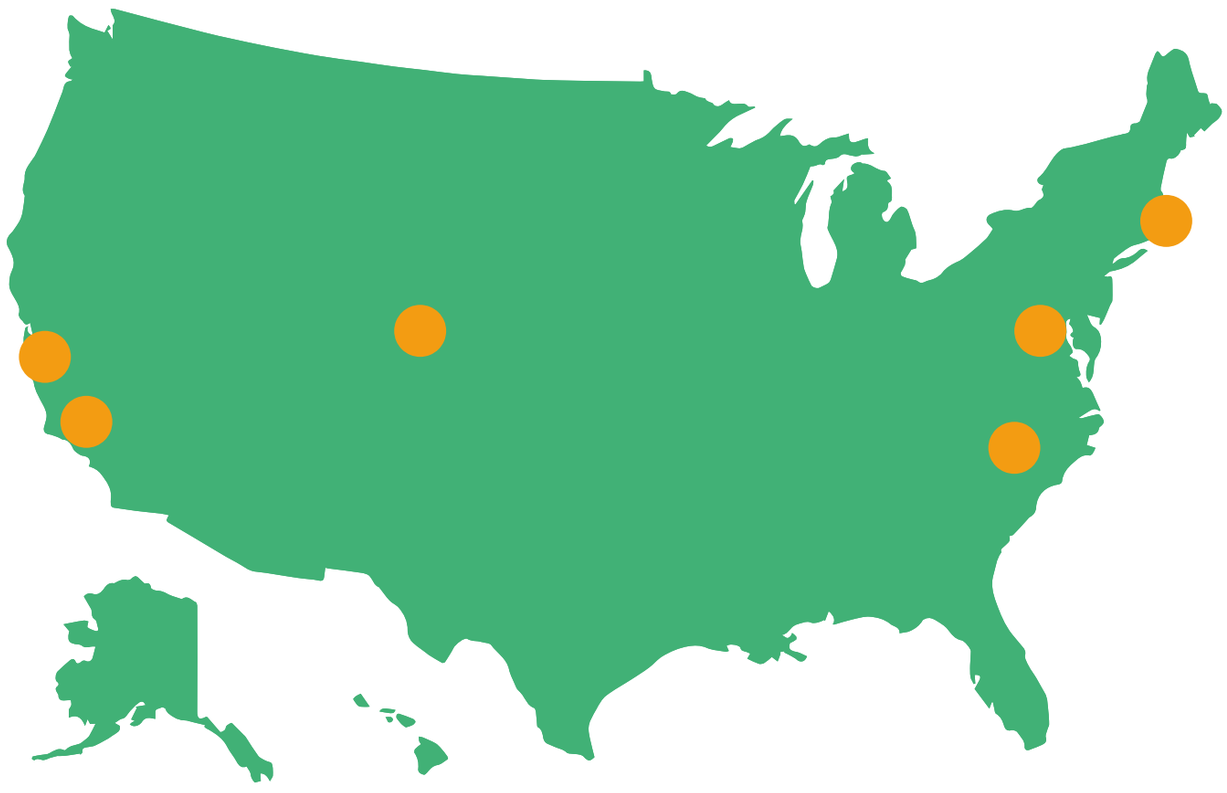

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