White Paper

Are You Ready for Novel Therapies? Building Out TechOps Capabilities to Sustain Commercial Delivery: Part 3

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Introduction

The following piece is the third part of a four-part series describing novel therapy supply chain archetypes, challenges, and potential management approaches.

- Part 1 introduced the four archetypes and their value chains: in vivo gene, ex vivo allogeneic, ex vivo autologous, and in vivo PCV therapies.
- Part 2 explained the archetypes' characteristics in more detail and how they differ from established supply chains for biologics.
- Part 3, below, outlines the supply chain challenges posed by the different archetypes and compares them with those of typical biologics supply chains.
- Part 4 will discuss how organizations can address the challenges facing novel therapy manufacturing and distribution. What considerations are involved in strategic decisions to develop a given novel therapy? How can companies develop required new technical operations capabilities?

Part 3: Supply Chain Characteristics by Archetype

In this part, we discuss the complexity and unique challenges that arise within the different archetypes along the three supply chain characteristics that we have identified: manufacturing and development, demand and replenishment, and logistics and providers. (See Exhibit 1.) Each of the sections below describes a set of challenges specific to the particular supply chain characteristic, and each begins with a description of how the challenge is typically handled within the biologic value chain as a basis for comparison.

Manufacturing and Development

Manufacturing and development present challenges along three criteria: manufacturing ingredients, labor and skill intensity, and lead-time constraints.

Exhibit 1 - Three Main Characteristics of Novel Therapy Supply Chains

Sources: Expert interviews, BCG experience.

Note: 4PL = fourth-party logistics.

Manufacturing Ingredients. We begin this list with manufacturing ingredients because all of the special supply chain characteristics and challenges outlined below—from production to the special handling that they require, from manufacturing to delivery—stem from the use of the basic materials used in all novel therapies. Whereas biologic medicines are often based on mammalian cells, novel therapies are created with human cells, plasmids, or viruses. Unlike biologics, these ingredients present the following challenges:

- GMP (good manufacturing practice)-grade plasmids and viral vector production are constrained by capacity and facility availability around the globe. Production is expensive and time-consuming.
- High input variability among patients makes it extremely difficult to put in place a robust, repeatable manufacturing and quality control process; many manufacturing runs are required to establish a reliable process and variability tolerance.
- Differences among operators in the way apheresis (collection of blood plasma) is done further increase variability of blood samples, creating a strong need to standardize this step across clinics where patient samples are collected.
- Containment, segregation, and line-clearance protocols for product changeover play a particularly important role in the handling of viruses due to strict biohazard controls. Some materials, such as adeno-associated viruses, are notoriously sticky and difficult to clean.

All four of the novel therapy archetypes involve either human cells or viruses in the production process and are subject to these challenges.

Human cells/Viruses
Human cells and viruses needed for the production process 1. Ex vivo allogeneic therapy 2. Ex vivo autologous therapy 3. In vivo gene therapy 4. PCV

Labor and Skill Intensity. Biologic manufacturing involves standardized production activities that are comparatively easy to scale and require minimal labor besides monitoring of the process. In contrast, the nature of novel therapies requires highly skilled labor for manufacture. This creates the following challenges:

- Manual manufacturing activities and the need for nonstop production increase labor and variable costs due to the need for highly skilled technicians, especially for ex vivo allogeneic, ex vivo autologous or gene therapy, and PCVs (personalized cancer vaccines).
- Testing costs are higher due to a lack of standardized product-characterization technologies. For example, highly customized or complex assays are required for assessing therapy structure and composition.
- A relatively immature ecosystem creates challenges for hiring and retaining talent. Companies can expect long lead times (up to nine months) for identifying and fully onboarding new hires or replacements.

The need for highly skilled labor applies to all of the novel therapy archetypes.

Scientific
Large amount of high-skilled labor required for manufacturing & release 1. Ex vivo allogeneic 2. Ex vivo autologous 3. In vivo gene 4. PCV

Treatment-Related Lead-Time Constraints. Manufacturing lead times for biologic production are less dependent on individual patients and are therefore not as difficult to manage. As a result, manufacturing steps are more predictable and easier to schedule for overall efficiency. The characteristics of certain novel therapies, in contrast, make lead times difficult to manage:

- Rapid evolution of the patient's condition creates stress due to urgent lead times for ex vivo autologous therapies, and companies must compete on "needle-to-needle" delivery speed.
- Some autologous (gene) therapies must compete with existing standards of care (e.g., blood transfusion). To encourage wide adoption, gene therapies thus need to be as comfortable and efficient as possible, for both patients and doctors.
- The use of human cells creates bottlenecks, as they are the starting input for the manufacturing process. The necessity to ship to distant, or even international, locations for processing extends lead times.
- Companies are paid only when the infusion is completed or when treatment milestones are achieved. The shorter the lead time, the earlier the revenue is received.

Ex vivo autologous and PCV therapies are subject to these challenges.

Time-critical
Critical lead time as manufacturing is kicked off with patient cells **2.** Ex vivo autologous **4.** PCV

Demand and Replenishment

Demand and replenishment considerations include demand pattern, inventory buildup, and production batch size.

Demand Pattern Over Life Cycle. Newly introduced biologics typically show a rapid growth in demand immediately following launch, with more stable demand through the remaining life cycle. Novel therapies face more unpredictable patterns:

- Doctors and hospitals are likely to wait to see if treatments are effective and if they are reimbursed by insurers, potentially causing initial demand uncertainty due to slow uptake.
- Aggressive sales plans combined with the inability to forecast demand accurately may lead to costly buildup of large safety stocks as a contingency buffer.
- In the near and mid-term, limited capacity will force companies to decide whether to prioritize commercial sales or a clinical program.

Ex vivo autologous gene and in vivo gene therapies in particular must contend with these challenges.

Unstable life cycle demand
Initial uncertain demand, with potential strong growth and long-lasting but smaller follow-up demand **2.** Ex vivo autologous gene therapy **3.** In vivo gene therapy

Opportunity to Build Up Inventory. Production of biologics allows for buildup of inventory ingredients and final products, enabling companies to develop economies of scale and absorb disruptions in supply chain or patient demand. Bespoke, single-patient novel therapies cannot be produced in volume or kept in inventory, making them vulnerable to the following risks:

- Manufacturers face high scheduling complexity due to the need to coordinate timing of manufacturing with incoming material and patient apheresis.
- Short-notice rebookings and cancellations by providers or patients could lead to unused manufacturing slots, resulting in higher cost of goods sold and forgone revenue.
- Companies may need to compensate by finding ways to quickly fill unused manufacturing slots or to build a queue of patients who are available on short notice.
- Production must adhere to strict treatment-center delivery timelines so the products do not expire and patient treatment windows are not missed.

Ex vivo autologous gene therapies and PCVs are particularly subject to these hazards.

Inventory

No opportunity to build up inventory

2. Ex vivo autologous gene therapy

4. PCV

Batch Size and Degree of Personalization. For traditional biologics, larger batches of the same product can be produced for different patients, enabling economies of scale. This is not possible with novel therapies:

- There are minimal opportunities to achieve economies of scale through production volume.
- Need to increase output and establish large facilities—with multiple individual suites, large amount of staff, and back-to-back shift manufacturing—results in high capital expenditures or cost of goods sold.
- Need for changeover (cleaning of equipment and room) after each patient batch reduces utilization of suites.
- Manufacturing and quality control must be done on an individual level, leading to the demand for many highly skilled—and hard-to-find—professionals.

These challenges apply to autologous gene therapies and PCVs.

Personalized batches

Personalized therapy requires small batch size for each drug (n=1)

2. Ex vivo autologous gene therapy

4. PCV

Logistics and Providers

This section covers the issues of fourth-party logistics (4PL) capabilities and provider collaboration.

Fourth-Party Logistics Tracking and Cold-Chain Capabilities. Although both biologics and novel therapies require the use of cold-chain procedures in the supply chain, distributors and logistics companies do not need specialized skills or complex cryopreservation technology to handle biologics shipments. Novel therapy supply chains, in contrast, demand complex handling:

- Logistics providers that can manage advanced chain-of-identity and cryopreserved transportation are still at an early stage, leading to limited choice of providers and ability to drive down costs.
- Transportation for autologous therapies and PCVs starts and ends with the patient, leading to multiple handoffs and exposing the supply chain to external factors, disruptions, and errors.
- Chain-of-identity and cold-chain logistics require real-time tracking capabilities and investment in IT systems and infrastructure and robust testing in extreme conditions—at the pharmaceutical company's expense.
- Logistics providers require intense protocol onboarding, contributing to complexity of launch and operations and driving up costs.

All novel therapy archetypes require cold-chain preservation in the supply chain. Autologous and in vivo PCV therapies must be manufactured and delivered with strict chain-of-identity controls throughout the process.

Cold chain	Chain of identity
Transport requires minimal temperature deviations **1.** Ex vivo allogeneic **2.** Ex vivo autologous **3.** In vivo gene **4.** PCV	Chain of identity must be maintained to ensure product reliability **2.** Ex vivo autologous **4.** PCV

Provider Connectedness and Collaboration. Despite the need to optimize for working capital and shelf life, biologic treatment success does not depend heavily on coordination in the supply chain between manufacturers and the provider ecosystem. Given the specialized nature of their materials and delivery, novel therapies pose unique challenges in this area:

- All providers must receive training on apheresis, drug storage, patient preparation and monitoring, and infusion protocols. This requires additional talent, driving up costs and operational complexity.
- New IT systems, such as portals for scheduling and tracking, and technologies like printers and scanners for labels must be installed at provider locations at pharmaceutical companies' expense.
- Many smaller hospitals are not equipped to store and handle cryopreserved drugs.

Connectivity and collaboration challenges primarily affect autologous and in vivo PCV therapies.

Provider integration
High integration with providers required for treatment success **2.** Ex vivo autologous **4.** PCV

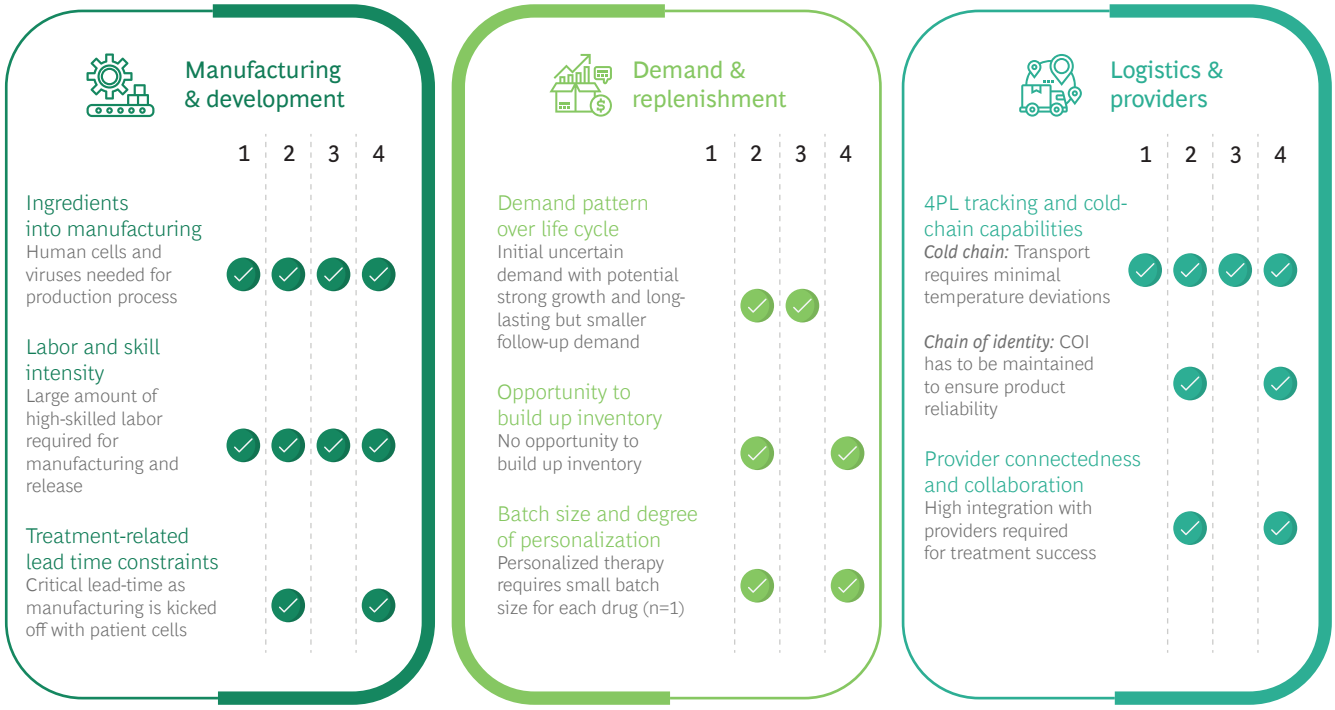
Conclusion

As we look more deeply into novel therapies' supply chain characteristics and their respective constraints, it's clear that manufacturing and delivery processes face a variety of specific challenges. Yet while there is a broad range of complex issues to be addressed, important themes are visible in the matrix that summarizes them (see Exhibit 2). In particular, the challenges presented by manufacturing ingredients, labor and skill intensity, and 4PL tracking and cold-chain capabilities affect all four of the novel therapy supply chain archetypes.

By looking down the columns of numbered archetypes in Exhibit 2, we can see that ex vivo autologous and PCV therapies (archetypes 2 and 4) are clearly the most complicated types of novel therapies to produce as they face nearly all of the challenges we've identified here.

In Part 4, we will wrap up the series with a description of strategic approaches pharmaceutical companies can take as they identify novel therapies to develop and seek to establish a competitive footprint in this complex and evolving environment.

Exhibit 2 - Overview: Challenges Affecting Supply Chain Archetypes



Sources: Expert interviews, BCG analysis.

Note: 1 = ex vivo allogeneic cell therapy; 2 = ex vivo autologous gene therapy; 3 = in vivo gene therapy; 4 = PCV; 4PL = fourth-party logistics provider.

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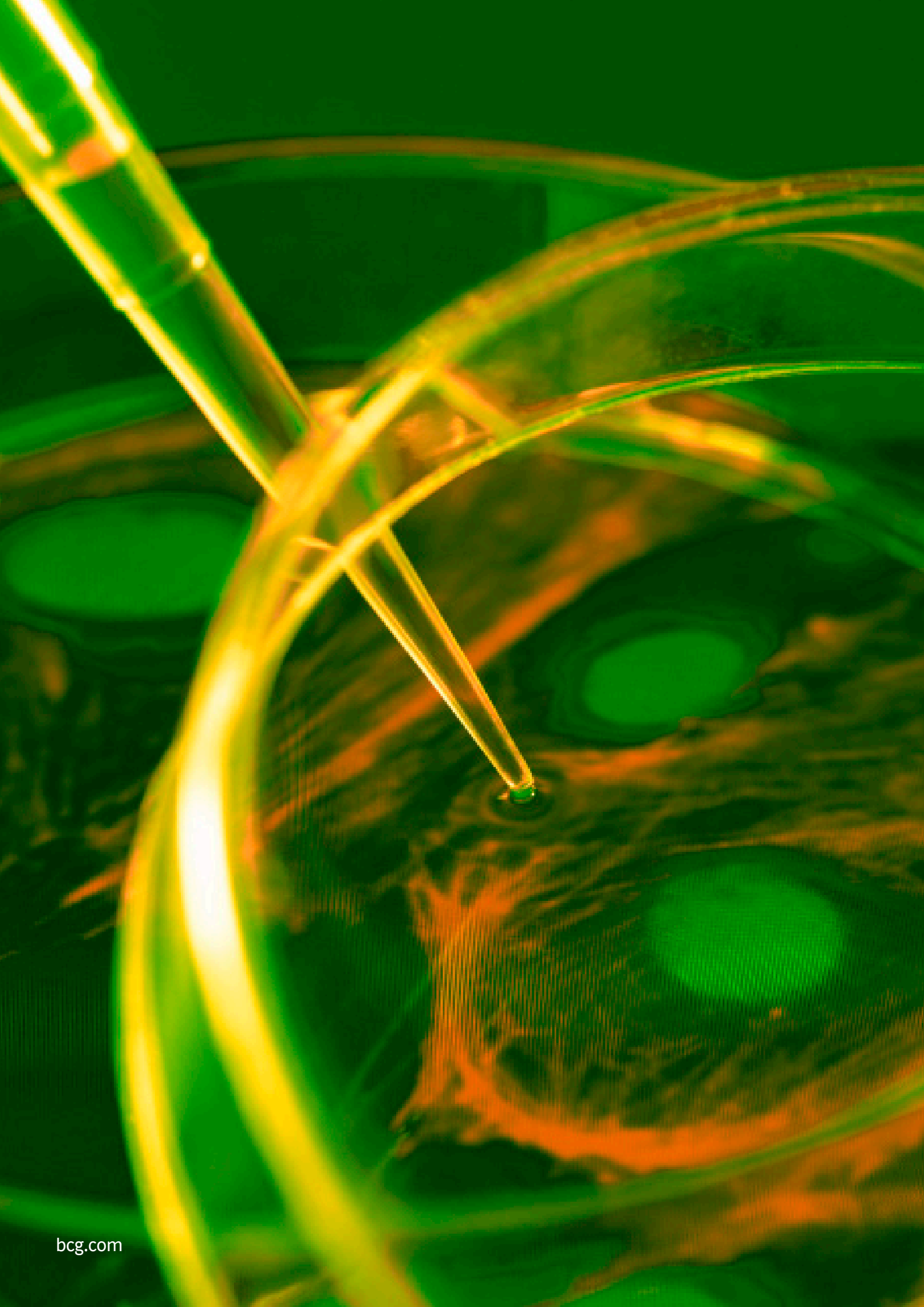

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