Manufacturing Cell Therapies: Development Strategies for Commercial Vision

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Summary

Developing and manufacturing a patient-specific cell therapy (PSCT) from clinical trials to a commercial product presents unique challenges. The right manufacturing process should take into account four key drivers—quality, cost of goods, sustainability, and scalability— to set the stage for a commercially viable product. Manufacturing systems must be methodically designed and engineered to control these drivers.

PCT

Progenitor Cell Therapy (PCT), a wholly-owned subsidiary of NeoStem, Inc., provides innovative solutions to the regenerative medicine industry. With PCT's more than 16 years of exclusive cell therapy-focused manufacturing and development experience, PCT helps biotechnology and cell therapy companies bridge the gap between therapy discovery and patient care by addressing the complex manufacturing challenges that stand in the way. PCT achieves this by offering a wide range of services: GMP manufacturing, manufacturing development services, cell and tissue processing, storage and distribution, and consulting and regulatory support. By utilizing PCT's expertise in some or all of these areas, cell therapy companies can focus on their core goal of developing effective clinical products while also planning for and advancing long-term goals for product quality, cost of goods, scalability, and sustainability.

Invetech

Invetech partners with global leaders in industry to deliver design and development, contract manufacturing, and custom automation services. Invetech provides client support along every step of the process, including brainstorming and product innovation, building and testing of prototypes, refining and streamlining of processes, and delivery of equipment and on-site training and support. They work with cell therapy clients to develop manufacturing equipment and strategies that maximize quality, scalability, and sustainability, with an eye towards cost-effectiveness and commercial viability. Invetech has been at the forefront of cell therapy process scale-up, automation, and disposables development for more than 10 years and has successfully completed projects in North America, Europe and Asia-Pacific.

Part 1: Cell Therapy Product Definition and Development

Before any company can begin manufacturing a therapy, or designing and engineering the production equipment, it is necessary to engage in detailed brainstorming and planning. You must first define your product—who do you want to serve, and what do you want your product to achieve?

Quality Target Product Profile

The FDA has provided draft guidance for creating a Target Product Profile (TPP) to document product attributes in a format that can evolve into the label claims for the product. While not required, a TPP or similar approach should be created and maintained by cell therapy developers. The FDA has also provided guidance via ICH Q8 for pharmaceutical development (where Quality by Design (QbD) principles are presented) for establishment of a Quality Target Product Profile (QTPP). Using the TPP as a key source of input, the QTPP is derived and maintained to detail the targeted post-manufacturing product attributes needed to support safety and efficacy of the product. While there is certainly latitude in how a QTPP is constructed, a recommended format provides the following categories of information:

- Characteristics profile (e.g. description, formulation, dosage, potency, volume, shelf life)
- Safety profile (e.g. microbial assurance, cellular impurities, manufacturing residuals)
- Use profile (e.g. indications for use, treatment timing, preparation and use)
- Business profile (e.g. geographies, market projections, clinical/commercial milestones, cost of goods targets, IP)

Often when cell therapy clients begin clinical development of a product, many of the elements of the QTPP are not fully known. Generally, the tendency is for the QTPP to be largely overlooked until a majority of the information can be specified, but that often leads to poor manufacturing development decisions that are regretted later on. The QTPP should be developed—at least as an initial draft—very early on, albeit with some areas that will need to be more thoroughly fleshed out at later stages. For example, elements of the business profile are often difficult to specify at an early stage of product development.

One last point is that, when developed early, the QTPP provides the input to establish a rational development plan that starts with the end in mind. The plan can then be confidently used to maintain strategic alignment among the ever-growing and ever-changing stakeholders as the therapeutic program develops, and to manage the risk of manufacturing development drifting away from the intended target. When a cell therapy developer is ready to engage external resources such as a contract development and manufacturing organization, this strategic alignment provides the right foundation for success.

As noted above, ICH Q8 guidance introduces QbD principles that can guide manufacturing development to meet product quality objectives. Development by Design (DbD) takes this one step further, whereby each of the critical aspects leading to viable commercial manufacturing are addressed, including not only quality, but also cost of goods (COGs), scalability, and sustainability.

Considering Each of the Development by Design Attributes and Their Challenges:

QUALITY: Quality is certainly foundational, as recognized by QbD, but for cell therapy—where there is heavy reliance on process to meet critical quality attributes (CQAs) of the final product—the manual, open, and human-dependent nature of many process steps presents substantial risk. Given that the process is only as strong as its weakest link, then, taking the example of a patient-specific product (where there is only one patient per lot), the strength of the process is directly related to reducing the risk of failing to treat the patient. Additionally, it is often impractical to perform the complete range of lot-release tests that would be required to confirm that all CQAs have been met for each lot; therefore, a robust process with validated ability to produce products of consistently high quality is critical. Automation, integration, and closed-system design are key tactics to elevate robustness of the process.

COGS (COST OF GOODS SOLD): The current high COGs of cell therapy products (typically driven by labor and testing costs for patient-specific products and by media for off-the-shelf products) usually demands a sizable commercial value proposition. As processes mature, the focus on COGs for commercial viability becomes critical. Development by Design allows for prospective approaches to addressing COGs appropriate for scale and stage of development.

SCALABILITY: Migrating from a clinical-scale process with the capacity to make tens to hundreds of patient doses per year, on to a commercial-scale process with the capacity to make thousands to ten-thousands of patient doses, can present significant comparability risks. In particular, cell therapy products inherently possess high complexity with one or more mechanisms of action that are often incompletely understood. In addition, there is currently a lack of analytical tools and *in vivo* models to judge product comparability.

SUSTAINABILITY: Finally, even if quality, COGs, and scale objectives have been met, there is the very real risk that manufacturing cannot be sustained over the full product life cycle. For example, a key risk is disruption in the relatively fragile and immature supply chain currently supporting cell therapy, which could halt manufacturing for an extended period of time. In the worst case, a process step relies on supply chain elements that become no longer available and requires changes to be developed, tested, and comparability demonstrated. To mitigate risks to sustainability, companies need to assess the full range of supply chain inputs to the manufacturing process, including reagents, consumables, equipment, and human resources. Additionally, the assessment should methodically include every unit operation, both process and testing.

Anticipating Comparability Risk

A key area that needs to be considered when looking at the four drivers of quality, cost, scalability, and sustainability is the potential comparability risk of making changes later on to address these drivers, and anticipating the implications. As noted by FDA, cell therapy developers must demonstrate that any manufacturing change does not affect safety, identity, purity, or potency. Depending on the nature of the change and the amount of product characterization, this demonstration of comparability between pre- and post-change product may only require laboratory testing or, at the other extreme, may require additional clinical studies. Early in a clinical development program, a change to the manufacturing process still presents comparability risk, but much less is at stake than with a change after substantial clinical data has been generated.

It's important to note that some changes in process have relatively low comparability risk, while others have relatively high risk. For example, changing a critical raw material in a core process step, such as going from animal serum to a serum-free material, would be a pretty major comparability risk, while the risk associated with switching from manual record keeping methods to electronic record keeping is fairly low. The risk is lower, generally, when the change does not alter the journey that the cells are on.

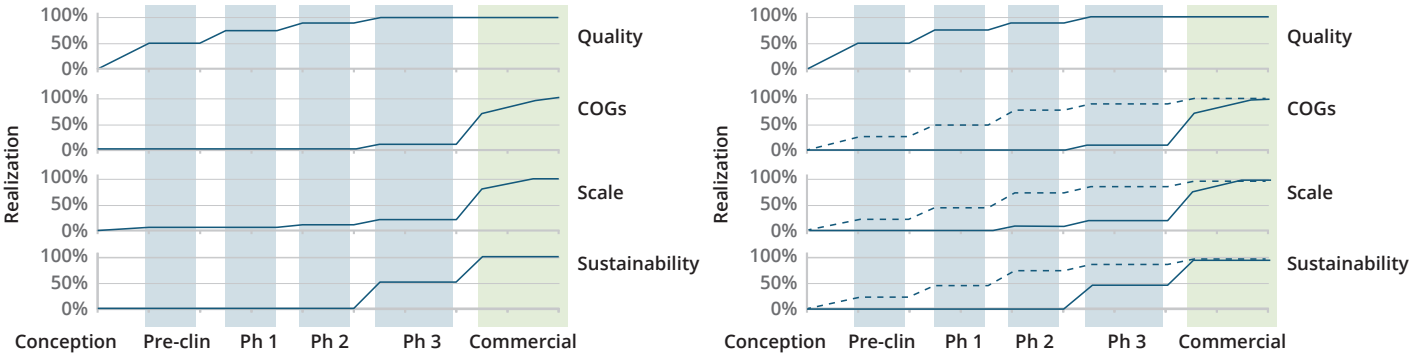
Managing Comparability Risk

RISK LEVEL	EXAMPLE	TIMING*
None	Automated sterility test	Before BLA
Low	Change in process unit op and "cell journey" is the same	Prior to 50% accrual in pivotal trials
Medium	Change in process unit op and "cell journey" is similar	Prior to initiation of pivotal trials
High	Change in process unit op and "cell journey" is modified	Some Phase 2 clinical data

**Timing for a complete change or an interim portion of the change that retires the comparability risk*

Advantages to Considering DbD Early

Considering DbD early on does not mean that a cell therapy developer needs to make a large investment much earlier on in the process, but it does mean they need to be planning ahead. Certainly, quality is a key focus from the start, but working through all of these areas mentioned at an early stage can provide significant cost and time advantages as a cell therapy developer moves further along the clinical process.



Development by Design: Initiate Early

CASE STUDY: PCT

Phase 2 trial rescue: the importance of QbD/DbD to maintain cell therapy product quality

A cell therapy developer completed a successful Phase 1 trial for their patient-specific cell therapy product. The developer sought the guidance and services of PCT after a subsequent Phase 2 trial was in danger of failing due to lower than expected efficacy outcomes and an unacceptable number of manufacturing failures. Of note, the original manufacturing process for the Phase 1 trial, conducted at a single site, was modified to facilitate multiple sites for the Phase 2 trial (e.g. increased manufacturing capacity), but was resulting in final products that failed to meet specifications. The trial was therefore halted and the client engaged PCT to systematically and rapidly evaluate the manufacturing process to minimize delay and cost impact to the clinical development of the client's therapy.

The first step was to break down the process into discrete unit operations (UO) and identify critical process parameters (CPP) for each. Changes to each UO and effect on CPPs were evaluated for impact on final product comparability between Phase 1 and Phase 2. Based on this impact assessment and a value assessment of specific changes, a revised process was established that was expected to maintain product comparability vs. Phase 1 and support the operational needs of the Phase 2 trial. Key elements of the revised process:

Definition of unit operation (UO): A defined activity or set of activities intended to accomplish a specific outcome based on use of specified materials, equipment, procedures, and personnel and performed within a surrounding environment.

- A UO incorporating an automated, closed separation system was implemented to replace a labor-intensive manual process with associated operator-driven variability and contamination risk.
- A UO that was critical to product quality initially required three repeats, four devices per repeat, 10 flasks per device with 10 x 106 cells per flask. Different volumes and cell concentrations were studied as alternatives. The resulting process required one repeat, two devices per repeat, 4 flasks per device with 150-200 x 106 cells per flask. Thus, the number of flasks that needed to be handled in this time-critical step was reduced from 120 down to 8.
- UOs used in the Phase 1 trial that were determined to be acceptable for the Phase 2 trial were restored without change.

Finally, a head-to-head comparability study between the original Phase 1 process and revised manufacturing process was performed by comparing three sample products produced by each process from common starting material. A prospectively determined decision tree mapped out the outcomes under which comparability would be shown and under what circumstances additional investigation would be required to determine comparability. Comparability to the original process was established and the trial successfully resumed using the revised process.

Subsequent to this project and noting lessons learned, the client engaged PCT to create a strategic manufacturing development plan for the client's product. The plan provides a roadmap to commercially viable manufacturing to guide change while avoiding the pitfalls that were experienced when the Phase 2 trial was first initiated. The plan addresses elements of development by design (DbD) including consistently high product quality with reasonable cost of goods that is able to meet demand over the commercial life of the product. The plan also identifies strategy to manage comparability risk, including prioritization of high-risk changes that are expected to have significant benefit to one or more DbD elements.

In terms of what a cell therapy developer can actually do to optimize the manufacturing process and maximize DbD, potential solutions might include sharing, integration, process automation, operational automation, and elimination—steps than can be very different, and have a different level of impact, when dealing with patient-specific cell therapies (PSCT) as opposed to pharmaceuticals. For example, one of the challenges with PSCT is that because each dose is for a separate patient, there is limited opportunity to share batches as one commonly would with pharmaceuticals to maximize cost-efficiency and scalability. The classic economies of scale are a challenge for PSCT, but there can be great payoff in integrating and automating processes. Elimination, especially, can be a key advantage when it comes to PSCT, as each hour saved by eliminating process steps is an hour saved on the individual production of each therapy for each patient, rather than merely one hour saved on the production of an entire batch of pharmaceuticals.

This discussion brings us to methods for optimizing DbD through the development of carefully thought out engineering and design strategies for developing cell therapy manufacturing systems.

Part 2: Cell Therapy Manufacturing System Engineering and Design

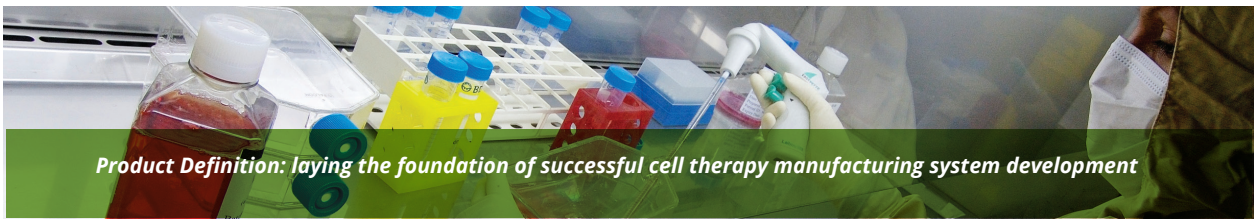
As with the manufacture of the cell therapy itself, successful development of a manufacturing system begins with the end in mind. The ultimate goal is to deliver a system that addresses the DbD principles mentioned previously, and the most likely way to meet that end goal is to have a clear idea of what you need before you even begin.

Product Definition: Laying the Foundations of Successful Cell Therapy Manufacturing System Development

A productive relationship between a manufacturing system developer and a client begins with visiting the client and observing their current manufacturing process. In Lean Manufacturing terminology, this is sometimes referred to as Going to the Gemba.

Cell therapy manufacturing can be an intensely manual and skill-based process that is not readily translatable into a consistent, affordable, repeatable, lower-cost manufacturing method. But as the vision is to ultimately treat patients at high volume in an affordable way, methods need to be identified to transform these processes into a series of repeatable, automated steps. The system developer should first look at possibilities for scaling or adapting currently available technology and systems, and then—only where required—apply invention, innovation, and development of new systems to maximize DbD.

For example, a cell therapy in clinical trials may take three people one week of processing in a biosafety cabinet in a clean room, in order to produce a single patient's batch of an autologous treatment. After a development project designed to transition this treatment procedure to manufacturing, a single operator may be capable of producing 20 patient batches in the same time period, using custom equipment and disposable processing sets in a lower-level clean environment.



Product Definition: laying the foundation of successful cell therapy manufacturing system development

Collaboration is Key in Cell Therapy Equipment Engineering and Manufacturing

Of course it is important to note here that it is not effective for a system developer to observe a client's process and then deliver a start-to-finish plan based solely on that observation. Rather, the system developer should work collaboratively with the client to complete a planning and feasibility study, which includes the observation phase discussed above. This study should occur early in the development of the cell therapy, ideally soon after the clinical manufacturing process is first defined. Results of the study should provide a long-term roadmap of how to achieve commercial-scale production. In addition to guiding the development of manufacturing, this roadmap provides a cell therapy developer with a clearer strategic vision to communicate to investors, partners, and other potential future stakeholders.

The planning and feasibility study involves regular communication between system developer and client. When the system developer first visits the client to observe their manufacturing process, the system developer should stay for one to two weeks and get to know the people and the process, and execute brainstorming and problem solving sessions on-site. Once the system developer leaves the client's location, it should continue to maintain open lines of communication with weekly conference calls and Web-based meetings to update the client on system development.

After initial observation, the system developer should work with the cell therapy client to engineer and create a manufacturing system that can help the client fulfill the needs established in the User Requirement Specification document (URS). The URS is a document that, most often, the client provides to the system developer, outlining the parameters of what the manufacturing system must be able to accomplish. For example, the URS might say that the end goal is to be able to treat 10,000 patients per year, at a cost of no more than $8,000 per patient, and that the therapeutic product must have a certain volume, cell count, and be shipped at a certain temperature, or other properties particular to that therapy. The system developer can then use the parameters found in the URS as design input for the engineering and design phase. In reality, larger, more experienced clients may come to a system developer with this document complete or nearly complete, so that it can be used as a roadmap in developing the system, while smaller biotech startups may not have had much experience with a URS and will need guidance in fleshing that document out before system design can even begin. In addition to the URS, there are other engineering operational documents, including the functional specification and software specification, which outline exactly what the system needs to do in order to deliver the performance that is requested in the URS. Ultimately, the URS becomes part of the engineering turnover package that a cell therapy developer will keep, and it can be shared with FDA upon request.

The Value of Prototyping and Validation Testing

Once concept development has taken place, comments and suggestions have been taken into account from both sides, and the system developer has incorporated the requirements of the URS and other technical documents, the system developer then builds a prototype or small-scale test version of the system based on all of the information gathered to date. These prototypes give the client the opportunity to see how elements of the system will actually work in practice, and to provide feedback on the concept feasibility and suggest refinements or modifications required for the selected system concept to function as conceived.

Verification testing documentation of cell expansion equipment at Invetech's development facilities

From here, the project enters the detail design phase, where the final system is developed and then undergoes validation testing. The first level of verification testing is the Factory Acceptance Testing (FAT), where the system is tested at the developer's facility to ensure that it meets the design requirements. The system is then shipped to the client's site, where it undergoes Site Acceptance Testing (SAT) to ensure the system performs as per the FAT. Once the system is installed on site, it undergoes three specific sets of tests: Installation Qualification, Operational Qualification, and Performance Qualification (IQ, OQ, and PQ, respectively). IQ seeks to make sure that once the system has been installed, all the elements of the system are correctly installed and established. Next, OQ is a functional test to ensure all elements of the system function as required and may involve running the system with water or substitute fluids to make sure the desired product is produced as the end result of the process. Finally, PQ testing involves operating the integrated system to ensure it performs as specified.

Throughout installation and qualification testing, the system developer should provide each cell therapy client with an on-site team of professionals to offer guidance and support until the client accepts that the manufacturing system is up and running smoothly.

Case Study, Invetech

Argos Therapeutics - Automated Cellular and RNA Processing System

Beginning in April 2004, Invetech collaborated with Argos Therapeutics to develop prototype manufacturing systems for the production of fully personalized immunotherapies based on Argos' Arcelis® technology platform.

The Invetech-designed system was intended as a platform solution for dendritic cell therapies and was initially developed to manufacture autologous immunotherapies to treat advanced kidney cancer (metastatic renal cell carcinoma) and HIV.

The success of this early prototyping activity has resulted in Argos advancing its lead product candidate, AGS-003, through late-stage clinical research and on to the final stages of the regulatory approval process.

Invetech recently announced an agreement to supply Argos with modular, readily scalable, and highly automated equipment able to facilitate simultaneous processing of multiple patient-specific therapies in the same clean room. The technology is designed to be rapidly expandable to accommodate anticipated increases in production volume, in order to support future global commercialization pending regulatory approvals.

Jeff Abbey, president and CEO of Argos, recently commented, "The Invetech team has supported our production goals in the past and we believe Invetech is uniquely positioned to deliver the range of technology solutions necessary to meet the specialized needs of commercializing products based on our Arcelis® technology platform."

The Advantage of Partnering with Experienced Cell Therapy and Equipment CMOs

As cell therapy developers move from one clinical phase to the next, it is vital to avoid the tunnel vision of focusing solely on successfully completing a trial. It is equally important to address your long-term goals, specifically: What do you want your product to achieve, who is your target patient population, and is your current process suited to commercialization?

One way to keep an eye on the bigger picture is to define your manufacturing process in terms of Development by Design—quality, cost, scalability, and sustainability. Using the combined expertise of a CMO that focuses on cell therapies and a development partner that specializes in manufacturing systems can provide cell therapy developers with the necessary insight to answer some of the tougher questions early on, before those questions become roadblocks on the path to success.

PCT and Invetech Announce Agreement to Develop Closed Processing System for Cell Therapy Manufacturing

New System Will Support Commercial-Scale Manufacturing of Cell Therapies and Other Patient-Specific Products

PCT, a wholly-owned subsidary of NeoStem, and Invetech, a global leader in instrument development, custom automation, and contract manufacturing, have announced an agreement for the development of a new closed processing system for cell therapy manufacturing. Under the Agreement, Invetech will provide system design and engineering development and PCT will develop applications for performing closed cell processing manipulations such as separation. The Agreement envisions NeoStem as the commercial supplier of the System, which would constitute its first branded entry into the cell therapy tools market.

The System will be applicable to a range of cell therapy processes in development and commercialization stages, and will consist of an instrumentation platform, disposable flow path, and operating and application software for automated execution of user-selected protocols. The System will provide a flexible small-scale process suitable for GMP manufacturing of autologous and other patient-specific products where small scale is full scale, while also supporting efficient development of processes at lower cost prior to transitioning to scaled volumes.

“We are pleased to be partnering with Invetech on the development of a new technology specifically designed to meet the needs of our clients as their cell therapy products progress through clinical trials on a path towards commercialization,” said Robert A. Preti, Ph.D., President of PCT and Chief Scientific Officer of NeoStem. “By combining PCT’s more than 15 years of process development and manufacturing experience with Invetech’s industry-leading automated processing device expertise, we hope to produce and potentially market a system that would deliver significant cost of goods, quality, and scaling benefits over existing manual, cleanroom-based processing strategies.”

“Working with PCT to create equipment that will deliver services to companies in the emerging cell therapy industry is exciting and satisfying,” said Richard Grant, Global Vice President, Cell Therapy division of Invetech. “Our team shares a common passion with PCT to grow the cell therapy industry by developing new technology to support successful product development and commercialization.”

Author Bios

Brian Hampson, VP of Manufacturing Development and Engineering at Progenitor Cell Therapy

Brian Hampson is tasked with leading PCT's newly created Center for Innovation and Engineering. The Center was created to help PCT's clients think beyond current practices and to develop long-term solutions to the unique challenges faced by the manufacturers of cell therapy products. PCT's solutions accelerate the use of automation, integration, closed processing and other strategies to address the important issues of scale up, cost of goods, quality control, and robustness of our client's manufacturing processes in anticipation of commercial success.

Brian has focused his career primarily on the development of first-generation products and related manufacturing processes for the medical and biotechnology markets. He brings an extensive background and broad knowledge of many technical disciplines, including control systems, process automation, software, fluid systems, cell culture processes, aseptic/closed-system processing, and single-use disposable systems.

Prior to joining PCT, Brian worked for two decades with Aastrom Biosciences in Ann Arbor, Michigan, where he held several positions, most recently as Senior Engineering Fellow, an executive-level engineering position tasked with providing strategic technical leadership to cell therapy manufacturing technology. He had previously held positions at Aastrom including Vice President, Product Development; Senior Director, Product Engineering; and Director, Instrumentation Development. Brian is a thought leader in the application of engineering principles and innovation for the needs of bioreactor systems and the manufacture of cell therapy products, and he was the chief architect for the pioneering patient-specific automation efforts that resulted in the Aastrom Replicell System (ARS).

Brian holds Bachelor of Science and Master of Engineering degrees in Electrical Engineering from Cornell University.

Richard Grant, Global Vice President of Cell Therapy at Invetech

Richard has more than 30 years of product development experience across biomedical, cell therapy and industrial products fields. A member of Invetech for more than 15 years, Richard has been instrumental in building Invetech's cell therapy automation capability and continues to have a deep involvement in projects ranging from drug discovery and cell separation instruments to functionally closed, automated cellular therapy production systems. Richard is a sought-after thought leader in the field of cell therapy production scale-up and presents regularly at conferences each year.

Richard was also responsible for establishing Invetech's San Diego office in 2007 where he held the role of Vice President & Operations Manager. Prior to joining Invetech, Richard worked as Engineering Manager at a number of companies including John Valves, Lock Focus, and Dorf Industries, where he was responsible for all product development and engineering services.

Richard holds a Bachelor of Engineering (Hons) from the University of Melbourne and is the holder of several patents across a range of fields including fluidics, mining, medical devices, molecular biology and cell therapy.

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