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REVIEW ARTICLES

Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities

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Abstract

Decentralized or "redistributed" manufacturing has the potential to revolutionize the manufacturing approach for cell and gene therapies (CGTs), moving away from the "Fordist" paradigm, delivering health care locally, customized to the end user and, by its very nature, overcoming many of the challenges associated with manufacturing and distribution of high volume goods. In departing from the traditional centralized model of manufacturing, decentralized manufacturing divides production across sites or geographic regions. This paradigm shift imposes significant structural and organisational changes on a business presenting both hidden challenges that must be addressed and opportunities to be embraced. By profoundly adapting business practices, significant advantages can be realized through a democratized value chain, creation of professional-level jobs without geographic restriction to the central hub and a flexibility in response to external pressures and demands. To realize these potential opportunities, however, advances in manufacturing technology and support systems are required, as well as significant changes in the way CGTs are regulated to facilitate multi-site manufacturing. Decentralized manufacturing is likely to be the manufacturing platform of choice for advanced health care therapies—in particular, those with a high degree of personalization. The future success of these promising products will be enhanced by adopting sound business strategies early in development. To realize the benefits that decentralized manufacturing of CGTs has to offer, it is important to examine both the risks and the substantial opportunities present. In this research, we examine both the challenges and the opportunities this shift in business strategy represents in an effort to maximize the success of adoption.

Key Words: *cell- and tissue-based therapy, commerce, decision-making, organizational innovation*

Introduction

Cell and gene therapies (CGTs) offer a range of promising ways to provide curative therapy for a multitude of conditions that would otherwise have few clinical options for treatment. CGTs as an umbrella term covers two broad categories of biological products. Cellular therapies contain cells or tissues that exert the desired mechanism of action (MOA) whilst gene therapies are defined as a recombinant nucleic acid(s) that elicit an effect through the unique nucleic acid sequence [1].

This curative nature moves away from the traditional pharmaceutical model of ongoing treatment, yet early promises have failed to deliver the desired clinical outcomes, primarily due to manufacturing, characterization, commercial and regulatory challenges. Decentralized manufacturing (DCM) describes the reversal of the historical trend toward central factory production in the post-"Fordist" model with the aim to reduce delivery time, transportation costs and increase agility and responsiveness to local requirements [2,3]. Utilizing DCM to manufacture these products presents an attractive solution for implementing the roll out of patient-specific CGTs primarily due to the benefits that reduced logistics and proximity brings to personalization and responsivity to patient needs.

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DCM splits production into various locations or regions. In doing so, significant advantages are gained such as democratized supply, creating jobs without geographic restriction to the central hub and allowing flexible responses to external pressures and demands. This comes with challenges that need to be addressed, including a reduction in oversight, development of new business and manufacturing models, decision-making and control by central management, which are traditionally critical in maintaining quality in health care product manufacturing.

Previously we explored paradigms that exist in the health care sector and how they can inform decentralized CGT manufacture. These paradigms can inform decision-making only so far and many barriers remain beyond those that are easily identifiable. In this article we examine the "invisible barriers" that obstruct the roll out of DCM of CGTs and how they might be overcome.

From cell expansion and process control to "smart factories"

There is a huge emerging opportunity in manufacturing for networked computers and hardware to improve the production process and supply chain. These combined technologies are termed "cyber-physical systems" and represent a method for networked machines to leverage collective computing power and interconnectivity with the end goal of intelligent and responsive systems [4]. The anticipated systems will govern themselves, take preventative or corrective actions without human intervention and coordinate supply chains automatically. The catalyst for this transformative change is the internet of things (IoT), physical objects with sensors and actuators linked through networks and the internet.

There has been a huge increase in interest toward the concept of these new interconnected industrial environments. IBM has termed these "Smart Factories," GE "Industrial Internet," and Airbus "The Factory of the Future," whereas German industry uses the term "Industrie 4.0" [5,6]. Definitions for exactly what these industrial environments should contain are instead broadly presented as concepts. These include next-generation manufacturing [4], logistics and supply chain management [5], smart networks, automation [7] and big data [8]. These key themes clearly represent a paradigm shift away from traditional "Fordist" centralized manufacturing mass production for mass consumption [9], but more importantly, they facilitate replicability of manufacturing quality across a network of manufacturing sites by removing communication and distance as an obstacle. We have previously investigated (along with the UK Engineering and Physical Sciences Research Council and the Redistributed Manufacturing in Healthcare Network) the concept of smart "Cell Microfactories," and the conceptual differences between a "smart factory" and a more traditional multi-facility model are presented in Figure 1.

The concept of a "smart cell factory" relies heavily on equipment connectivity, with a particular focus on the expansion technology. This is a pivotal component of a successful CGT manufacturing chain and becomes increasingly important for DCM as variation between sites cannot be tolerated. Aside from the common comparability and quality control concerns, other components of the User Requirement Specifications for cell expansion technologies are likely to be different for allogeneic and autologous CGT products. For autologous CGT products, operational flexibility and modularity (for line segregation) are likely to be key drivers due to patient-specific requirements and input material variability, whereas for allogeneic CGT products scalability and achievable cell yield are likely to be the key drivers when choosing expansion technologies so that changes to demand can be managed.

In all cases, most unit operations can now be operated as closed systems so that the risk of potential batch loss due to infection is minimized. Many unit operations are still highly manual and labor-intensive, which gives rise to user variability. DCM processes by their nature increase geographic distance while reducing the information flow and oversight that dictates standards. This can lead to the exacerbation of user variability issues [10]. Thus, automation of the key unit operations has been identified as a key facilitator of any DCM opportunities [11]. It is clear that smart factories present a huge opportunity to revolutionize CGT production, but technology is still under development. Candidate manufacturing platforms that possess key features suiting them to DCM are outlined in Table I. These systems have the potential to aid the DCM process by meeting individual customer requirements, obtaining efficiency through automation, modularity and enabling flexibility, to both scheduled and unscheduled manufacturing processes deviations [22].

Decentralization of skilled labor

Since the 19th-century experiences with the Luddites [23], the move toward fully automated systems has been viewed with distrust by the labor market [24]. Unlike centralized manufacturing, which concentrates labor and in turn pools the collective expertise, DCM relies on portioning out the workforce into tranches of skilled operators, as outlined in Figure 2. These human teams may be resident at the manufacturing site or act as "roving labor" but must augment

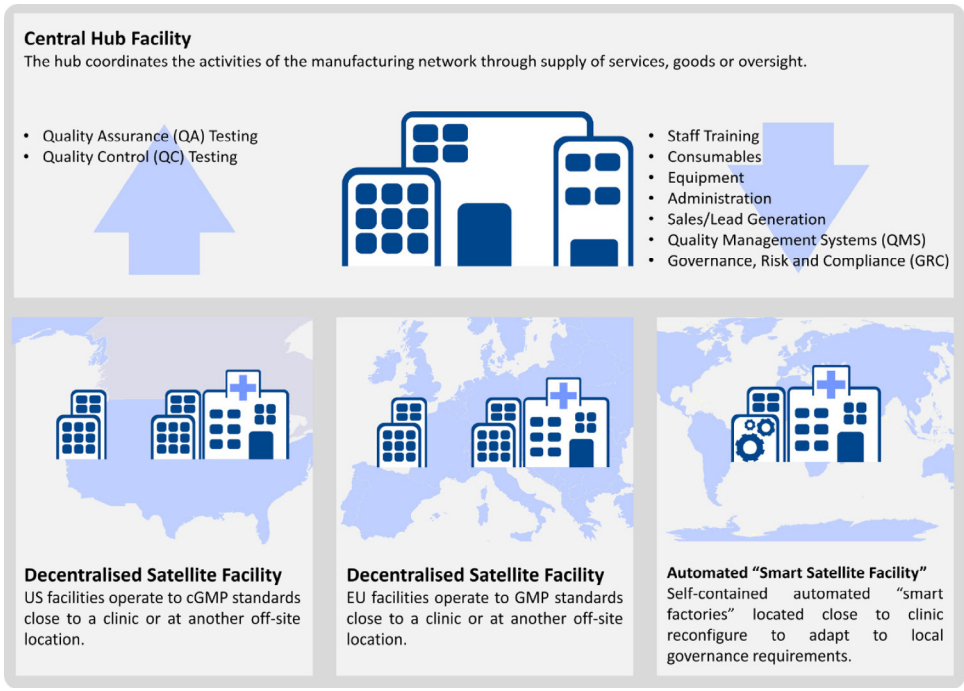

Figure 1. Decentralized manufacturing strategies for CGTs. Satellite facilities may operate in stand-alone locations or close-to-clinic. The automated "smart satellite facility" forgoes the complexities of a large staffed facility, instead externalizing and automating processes and services to reduce the geographic pressures that affect facility location.

the automated platforms to provide an equivalent labor pool, albeit at a reduced scale, to a centralized factory. These teams are likely to have fewer operators with high technical expertise per member. This makes the manufacturing capacity vulnerable to external stresses such as staff sickness or turnover. Thus, staff must be highly motivated and committed to succeed by being part of a bottom-up managerial approach and, preferably, part of an enterprise network. The benefits of a well-constructed enterprise will be manifested in reduced operational overheads and an increased resilience to external market stresses due to increased awareness of valuable locally sourced information [25].

The hallmarks of good human operators, ingenuity and situational awareness are vital for CGT manufacture as a high degree of technical expertise is required to understand the failure modes that may result from process deviations and to take steps to mitigate them. However, the precision and repeatability offered by automation is key to effective CGT manufacturing control at multiple sites. Tasks must be automated to constrain the process within the design space, but skilled human operators are required to determine whether deviations from sources such as raw material variation are sufficient to prevent the process from delivering acceptable product. Additionally, for the foreseeable future, any automated solutions will require human intervention in the event of a systems failure. Retaining a skilled workforce with knowledge of the infrastructure and discretionary expertise for corrective action is vital for mitigating this risk.

The precise format of DCM is yet to be established, but it is clear it will require skilled technical operators or process engineers to manage the production systems and potentially scientists to perform quality control operations [26]. The labor requirements of DCM are a double-edged sword. The keen opportunities yielded by geographically distributing your labor base are tempered by the very real threat of a poor skills pool and an aging workforce in a localized economy [27]. It is possible these weaknesses could be ameliorated through a combination of a judicial use of remuneration packages combined with a roving technical workforce able to fill gaps in expertise from site to site. The allocation of labor between automated platforms and human operators is still a relatively novel concept, even more so when discussing interconnected responsive systems. However, simulation-based models that simulate the ideal working relationship to be struck between these two process constituents are emerging [28].

Management of challenging value chains

Management of the complex transport and distribution needs of CGT products, such as their key paradigm blood, is a key decision when considering decentralization [29]. Traditional pharmaceuticals are,

Table I. Current automated culture platforms that may be adapted to decentralized manufacturing of CGTs.

Platform	Research group or company	Key features	Ref
ambr 250	Sartorius Stedim (formerly TAP Biosystems)	• Closed parallel loop design • Can be integrated with other analysis equipment • Modular production platform for multiple batches • Microcarrier/suspension culture allows high density culture • Clinical-grade output	[12]
Aastrom Replicell System (ARS)	Vericel Corporation (formerly Aastrom Biosciences, Inc.)	• Closed loop, single-use culture cassette and transport pack • Automated protocols for cell washing and expansion • Modular platform can accept multiple cassettes for multiple batches • Planar cassettes limit expansion potential • Clinical-grade output	[13]
R-CPX: Robotized Cell Processing eXpert system	Kawasaki Heavy Industries Ltd. with National Institute of Advanced Industrial Science and Technology (AIST, Japan)	• Fully automated process with human "pass box" to enable diverse usage • Image processing for cell assessment • Ability to handle multiple product streams • Flexible production scheduling	[14]
Octane Cocoon	Octane Biotech, Inc.	• Pod-like closed manufacturing unit can be run in lower classification environments • Internal cassette structure • Product made in clearly separated units which can be scaled out • Fully automated expansion process	[15]
"Kotozukuri" (construction of a industrial system to connect all the essential processes) flexible Modular Platform (fMP)	Osaka University (Professors M. Kino-Oka)	• Normalization of fluidics, handling and transfers • Self-contained microfactory system • Manages its own atmospheric environment through proprietary interlocks • Reconfiguration of isolators, permits different production layouts from single micro-factory	[16]
SelecT® Systems	Sartorius Stedim (formerly TAP Biosystems)	• T-flask handling • Multiple cell line handling • Validatable • Plating options • Reproducible liquid handling • Currently out of production	[17]
Quantum® Cell Expansion System	Terumo BCT	• Hollow fiber reactor mimics flask culture • Scale out approach • Semi-automated; one operator can handle 10 reactors • Closed system with small footprint	[18]
Fully automated "Smart Cell Factory"	Tokyo Electron Limited (TEL)	• Colony isolation with automated cell picking and culture • Standardized bespoke culture plates to normalize colony conditions • Automated image analysis quality assurance • Clinical grade output	[19]
AUTOSTEM StemCell/ StromalCell Factory	AUTOSTEM Consortium	• Closed process from donor harvest to product delivery • Functional surface fibroblast colony-forming units selection • *In situ* sensors for process control	[20]
CliniMACS Progidy	Miltenyi Biotec	• Modular platform can be reconfigured for differing workflows • Multiple cell line handling • "All-in-one" approach integrates cell separation, magnetic cell sorting and cell culture	[21]

on the whole, thermally stable formulaic products, whereas CGTs are more similar to blood products in their distribution model, and it has been suggested that distribution of CGTs could be simplified by leveraging existing infrastructure of tissue banks [30] and distribution networks to accelerate transition to therapy [31]. Historically, regenerative medicine products can suffer from high product loss [32]. Lessons can be learned from the successes of the blood transport network, which estimates waste to be relatively low at 2% [33]. Reliance on single sources for mission-critical constituents must be avoided because, in the event of an interruption to supply, these could completely stall production at more than one company.

The supply chain and logistics of CGT products is currently an area that requires further research and development activity [34]. As therapies have moved toward clinical trials, little time has been spent beyond

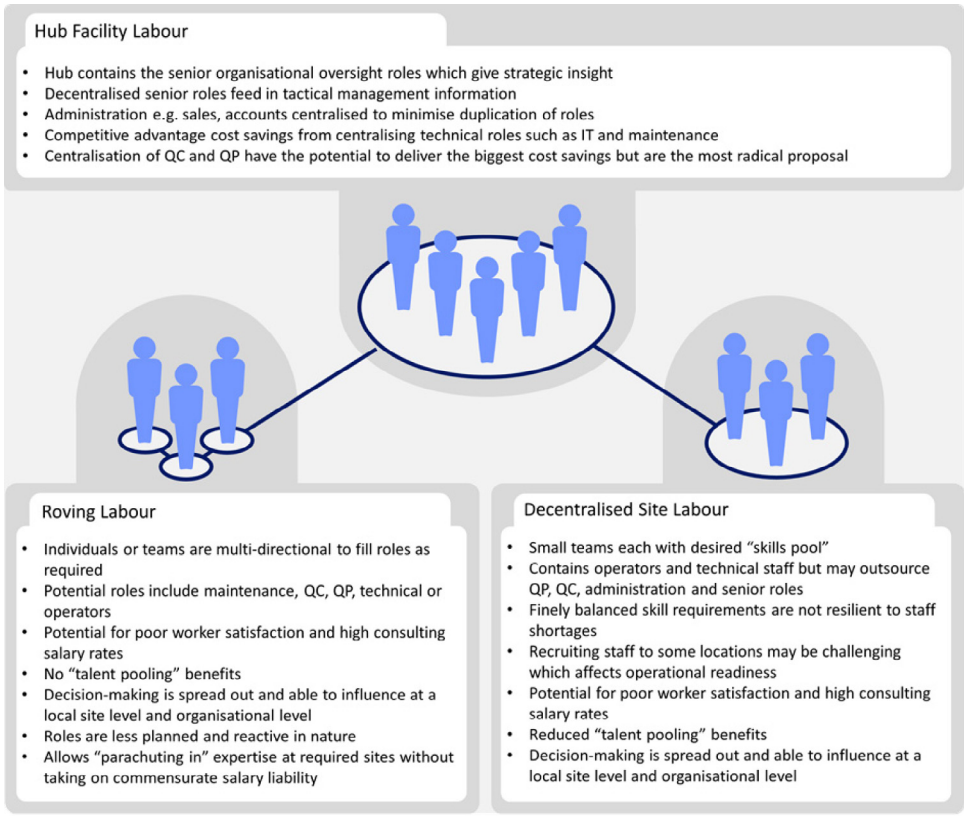

Figure 2. Allocation of labor for decentralized manufacturing of CGTs. Skilled labor will be required throughout the decentralized network. Geographic availability of skilled labor can affect siting of manufacturing "nodes," but any shortfall can be substituted with roving labor if it is not punitively costly.

the mandatory transit trials on developing an understanding of how product should best be shipped and handled or whether this could affect indicators of cell function [35]. This is less of an issue for blood products because they have shelf lives that allow for modest delays in the distribution process. The transit window for CGTs and precursor material, however, is likely to be more stringent and thus the pressure to situate closer to clinic higher. Although some technologies, such as plant- or animal-derived antifreeze proteins, act as enablers, without significant progress in storage technologies for fresh CGTs, the options for long-term management of inventory remain limited to low temperature cryopreservation [36]. This raises another barrier that must be overcome when penetrating a market in which few clinics possess liquid nitrogen storage or –80°C freezers in their pharmacies [37]. DCM overcomes this problem by situating manufacturing close to clinic, minimizing bi-directional transit from initial sourcing to delivery of final product.

Traditional models of production, supply and demand rely on historical data, which works well for high-volume, predictable demand patterns commoditized products, such as vaccines but will not work as well for low-volume, personalized products such as autologous CGTs or tissue engineered products [38]. In the consumer product space, purchase-activated manufacturing has been used to develop a customized retail product by delivering the personalization steps at the point of request [39]. For CGT manufacturing, this could more easily be viewed as a "postponed manufacturing approach" in which a generic intermediate product (e.g., vials of a working cell bank) is finished with personalizing steps such as transfection and formulation at the decentralized site. This is particularly relevant to the exemplar of tissue engineering, which might use a biomaterial supplemented with patient-specific material at the point of use. This could consist of an approved off-the-shelf synthetic polymer such as polyethylene glycol (PEG) [40], poly(lactic-co-glycolic acid) (PLGA) [41], polycaprolactone (PCL), and ultra-high molecular weight polyethylene (UHMWPE) [42] or alternatively a naturally derived polymer [43] or patient tissue [44].

Can CGT manufacturing, which is inherently sensitive to time pressures, tolerate a pause step pending detail about the degree of product personalization that is required? The answer to this question is a trade-off between reduced efficacy due to the delay and

increased utility due to the personalization, which may be in the form of a modified product or, indeed, modified usage. Technical requirements of a pause step for fresh CGT are challenging, and it may be simpler instead to apply the principles of agile manufacturing to re-engineer the process chain toward a method in which the customization information is received and enacted earlier [45].

An operational simulation will help the design of these agile systems. The complex interrelations between DCM decision-making steps make modeling the process particularly challenging. A large number of potential supply chain models are available, including deterministic analytical models, in which the variables are both known and specified [46], stochastic analytical models where a minimum of one variable is unknown but is assumed to follow a specified distribution [47], economic models for modeling the buyer–supplier relationship [48] and simulation models that model increased demand [49].

Of these potential models, stochastic models represent the closest working "prototype" on which to base DCM of CGTs [50]. These models typically have at least one unknown variable, such as the predicted production time, but follow probability distributions to estimate probable outcomes and the best scheduling methods. Many of these examine the process for a traditional stable product in a centralized model, but there are DCM approaches that focus specifically on deteriorating inventory that could be adapted for CGTs [51]. It is important to remember that although responsiveness is desirable, it must not act to delay procurement of materials. Thus, any model must predict material requirements, consider personalization features and weigh both these factors against cost and efficacy—no small feat. With a model framework established, Kanban principles that act as a material flow control mechanism to enact small, low resistance, high-impact changes could be used to stratify supply chain constraints and establish what can be done to optimize the distribution as a whole [52].

CGT manufacturing and supply will be demand driven, not only for the product itself but also potentially late-stage customization requests. It is attractive to envision a DCM system with just-in-time supply of critical components, agile and responsive to hospital procurement by the reduction in logistics due to the proximity of the clinic. Joining these systems will undoubtedly be a significant challenge, but reassuring technological advancements from the consumer space have reinforced its promise.

Opportunities for socioeconomic impact

DCM has the potential to transcend the traditional manufacturing value chain and deliver additional socioeconomic benefits. Yet in doing so, the radical change in therapeutic offering will challenge our accepted view and practices in health care.

Following the launch of Sovaldi and subsequently Harvoni for treating hepatitis C [53], one-off curative treatments are becoming more accepted and familiar. The disbursement of these therapeutics is limited by their extremely high price tags of $84,000 and $94,500 for treatment, respectively. This extremely high cost compared with a chemotherapeutic agent costing $500 to $10,000 per month is due in part to the single rather than continuous reimbursement structure required for these treatments [53]. Although the upfront figure is admittedly high, when examining the quality adjusted life years (a method to normalize health care treatment costs by measuring against relative life years gained), these treatments actually score favorably. This has not prevented a number of groups including the U.S. Congress calling these prices "unsustainable" and "too high" [53].

Given the experience with Sovaldi and Harvoni, it is important to keep in mind that the reimbursement strategies for curative drugs are likely to be similar to CGT curative therapies. The challenge for CGT manufacturing in general must be to avoid disillusionment and accusations of unreasonable profits with the industry. The reasons for these costs should be clearly justified and reimbursement strategies for high upfront costs rationalized in terms of whole treatment cycle. Could a "localism" approach to manufacturing act to ameliorate the (often) unfair image of "big pharma"?

DCM can be supported by off-site activities, but locating the majority of production and servicing activities close to the end user has the highest potential to increase added value [54]. This model departs from the conventional wisdom of traditional centralized manufacturing and reimbursement could present challenges because of the dispersed ownership of the chain of custody. It is possible that there may be a stratification of ownership with an innovating company supplying a clinical customer with the final product and owning all aspects of the manufacturing chain. Alternatively, a customer may be purchasing the final product from an intermediary company that has a right to manufacture the product, licensed from the innovator, on its proprietary manufacturing platform similarly to a franchised operation. This may allow payments to be split between multiple parties thus reducing exposure to the high upfront investment costs that are incurred for new plant. Moreover, systems like the United Kingdom's National Health Service that provide free treatment at the point of care may fit well with this approach, allowing uptake of CGT manufacturing without large initial capital expenditure, instead relying on smaller payments that are more in

line with currently accepted reimbursement models for pharmaceuticals. This health care provisioning model could be a similar program to the "Commissioning Through Evaluation' program, which centrally funds emerging treatments for evaluation purposes.

To be effective, DCM must use measures to ensure reliability of process output from site to site. Depending on the extent to which such measure externalize the skills required to execute the manufacture, such an arrangement has the potential to generate jobs in a GMP setting at higher value levels than commodity manufacturing but without necessarily requiring the full skill set of a cell biologist.

Systems and technical security

The industrial gains of the 21st century came from interactions between human input and the capability of mechanical systems. With the advent of the connected cyber-physical systems, decision-making and oversight is removed from human operators, yielding benefits in speed, efficiency and cost. The drawback of this is that it opens avenues of attack for cyber threats. The year 2010 represented a turning point for industrial systems security with the discovery of the Stuxnet worm. Stuxnet was different from previous malicious software in that it appeared to be created by a well-resourced government-backed group whose sole purpose was destruction of physical equipment [55]. DCM relies heavily on interconnected systems, removing people from decision-making processes and automating production. These characteristics render it particularly susceptible to malicious intervention, and steps must be taken to either to secure communication or isolate from external influence.

It was recognized nearly 40 years ago that the use of computer systems in medicine was increasing to the point where computer systems had a significant effect on patient care. As such, the question of who is at fault when it is the computer, rather than the medical practitioner, that makes a mistake needed to be considered [56]. This was tested following the 1985–1987 Therac-25 radiotherapy machine accidents that gave substantial overdoses to patients due to malfunction. This resulted in injury and fatalities over an overly long period while software bugs were identified [57]. Most commercial software contains flaws or defects that can be reduced (but not eliminated) by adopting software assurance processes [58]. This task has become ever more challenging as technical advances add successive layers of complexity to software. Currently the area is lightly regulated both in the United States and European Union because it is widely considered that regulation stifles innovation within software firms [59,60]. Consequently, the majority of software legal precedents have not evolved since the 1980s, and legal proceedings rely on contract law, tort law or both [59].

In addition to malicious security concerns, there are legitimate concerns over both organizational deceit and counterfeiting. Organizational deception has been suggested as the root cause of recent high-profile industrial manufacturing cases [61]; this can be limited by managing expectation of the business [62] but should be of limited potential due to the rigor of Good Manufacturing Practice compliance auditing [61]. Serialization of completed products to certify authenticity can instill confidence in the final stages of the supply chain, but this does not consider the stages of the supply chain before its completion, only its destination to the end user. Supply chains have evolved and firms are not limited to one country or economy [63]. This provides enormous benefits to companies, but auditing all suppliers to an acceptable standard becomes a daunting task and one that has not always been successful, as was learned in the 2008 tainted heparin case [64].

Ensuring the security of both the manufacturing process and the supply chain supporting it are essential for achieving quality products. Supply chain management becomes increasingly challenging when cooperation between partners is low as demonstrated by the difficulties between the Chinese and American regulators during the 2008 heparin crisis. As sites will be geographically separated, DCM is particularly susceptible to deviations from specification and business practices must be geared specifically toward avoiding this. Communication will need to be seamless not just between echelons of the company, but between suppliers, regulators, customers and health care professionals.

Responsibilities, rights and regulatory understanding

DCM, by its very nature, reduces temporal differences between the manufacturing facility and the consumer, thus allowing fundamental improvements in process due to proximity. Clearly this creates a significant challenge in oversight and management. Facilities may become fragmented with each becoming isolated within the larger network. If each is treated in isolation or is unaware of responsibilities across the network, the facility is unlikely to be able to suggest or make even minor improvements in the network, an important consideration given the GMP mandate for continual improvement without impact to product. For this reason, it is essential that each member of the DCM network is aware of its role and the broader activities of the network as well as maintaining communication potentially through automated update propagation measures [10,65,66].

Sociotechnical system theory suggests organizations have two sides: the technical side and the human side [67]. For DCM, the essential role of the human side is defining the patient-product requirements. This is complemented by the technical (cyber/physical systems) that mandate specification and ensure compliance. The opportunity to really permit DCM while maintaining oversight and management stems from the "smart factory" architecture in the form of integrated management systems and governance, risk and compliance systems (GRC) that communicate across and between sites. Integration of management systems is largely theoretical, but models on which to base thinking do exist [68]. Similarly, a number of theoretical frameworks for GRC have emerged over the past decade [66]. The key features of these systems are a drive to manage stakeholder requirements in a more systematic manner, optimizing the whole network, as opposed to just locally. Implementation of these systems will primarily be driven by potential cost reductions, as has been the case in existing health care settings [65], the benefit of which is proportionately larger for a DCM organization as each facility would forgo expensive human roles in place of an information technology–based solution.

Responsibilities of companies or individuals toward aspects of a DCM network are unclear. CGT development is largely pursued by small to medium-sized enterprises (SMEs) [69], thus it is likely that a manufacturing process would involve more than one stakeholder with shared commercial rights to the process, technology or product. Infrastructure investments are costly, and it is feasible that a manufacturing chain could be tooled to create multiple product types for multiple stakeholders. This would share the cost but also necessitate shared responsibility for rigorous manufacturing and a mutually satisfactory agreement between regulators and manufacturers concerning the burden of proof to ensure comparability between sites.

The recent position paper on the regulatory approach to additive manufacturing [70] highlights the challenges that DCM will encounter in the context of the customizable features of the product. In particular, product and process characterization and validation were identified as key obstacles. For a network of DCM hubs, this would be further complicated by the need to ensure that quality management systems and validation methods remain comparable between sites. This involves ensuring that there is no significant equipment variation between sites and applying quality standards consistently throughout the network, preferably using a boilerplate quality management systems. A vital consideration is that of the managing liability if faults do occur. Is the equipment manufacturer responsible for a software or hardware fault that affects the clinical outcome? Previous instances would suggest this to be the case, and therefore manufacturers must take reasonable steps to mitigate risk [59]. Emerging frameworks for responsible innovation could be used both to mitigate the risk and to reinforce the argument for novel scientific practices such as CGTs [71].

Perspectives

Local manufacturing was historically the choice for supplying goods to a region. This only changed with the advent of the industrial revolution and the significant cost savings associated with large production volumes have kept this trend in place ever since. Many CGTs represent a low-volume/high-margin product that cannot easily be produced at scale with current technologies. This may change as our understanding of process engineering for scale-up technologies such as stirred tank reactors progresses [72], but some production systems particularly those aimed at the autologous segment will by their very nature remain scaled-out, small-lot-size production volumes [73]. The degree of patient material used in the manufacturing process combined with local personalization steps add another factor that complicates the case for centralized manufacturing of CGTs.

One of the key drawbacks for current cell-based therapeutics is the unsuitability of many existing culture methods for scale-up. Small-scale modular manufacturing systems with integrated real-time analysis and control techniques are the technological solution, but this is a small component of the bigger picture. The true revolutionary catalyst for enabling DCM is interconnected industrial environments. These will not only revolutionize the manufacturing value chain but, more importantly, the governance and risk management of CGT manufacture. The potential for integration of these interconnected systems is presented in Figure 3. The effects on the value chain to reliably achieve consistency cannot and should not be undersold. Connected systems with heavily automated solutions have the potential to revolutionize manufacturing) and act as a significant enabler for DCM because it provides the confidence in the product at each site for the release and subsequent reimbursement to take place. The development and roll out of these interconnected industrial environments are key enablers for DCM and will drive not only manufacturing improvements but also process and product confidence.

Engineered platforms for manufacturing and analysis are usually developed by different companies, often ending up being used for purposes unrelated to their eventual use. This has led to the creation of the hardware and software components making up manufacturing and analysis platforms differing widely

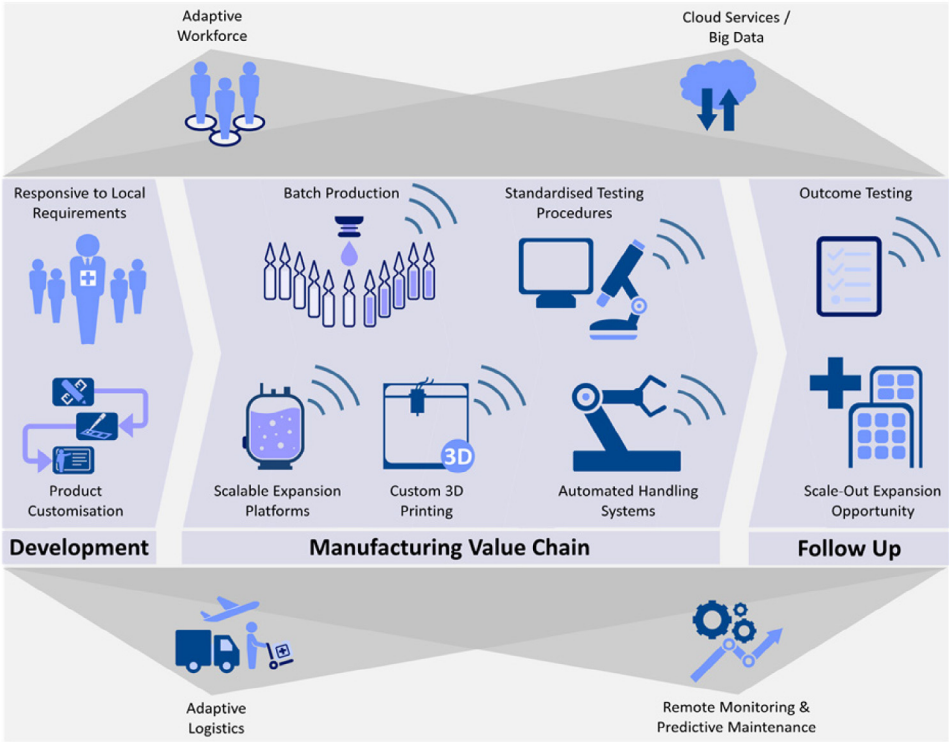

Figure 3. Aspects of the manufacturing value chain for decentralized CGTs. Notable are the high degree of interconnectivity between discreet aspects of the value chain incorporating aspects of the IoT signified by the wireless icon. This includes not only the hardware component of manufacturing systems but also the outcome testing that feeds back into the production value chain. Core aspects that act as enablers for DCM including the adaptive workforce, cloud services/big data, adaptive logistics and remote monitoring and predictive maintenance are important over the whole manufacturing value chain.

and the development of proprietary protocols or interfaces that are incompatible for the purpose of rapid data exchange. This takes a substantial toll on productivity in health care environments and is a major barrier for fully automated solutions where each component in a process chain needs to "talk" seamlessly to its dependents without requiring human input—the so-called internet-of-things (IoT). This networked approach allows the sensory information from all aspects of the network to be collected, logged and dynamically adjusted with potentially vast savings to be made in production and maintenance optimization. Although interoperability has been largely successful for consumer products, it is still lacking from many commercial systems in a health care setting. These include both low-cost/low-technology products such as blood or glucose analyzers to high-cost/high-technology diagnostic magnetic resonance imaging and computed tomography machines [74]. Achieving a similar level or seamless connectivity between equipment vital for CGT manufacturing requires not only technical expertise, but a shift in business practice to limit "gag clauses," or provisions that prevent sharing of information [74]. As members of the practitioner community become more aware of the advantages a standardized plug-and-play system has to their shared business interests, we expect to see an emergence of accepted operation and manufacture. This will accelerate the translation of innovative products because researchers will be undertaking research bearing in mind these operational paradigms.

In addition to all of the technical considerations, there remain significant questions around regulation. Is a qualified person, or QP, required at each site, and are all sites required to cease production during a process changeover? There are currently no answers to these questions, but they are vital aspects to ensuring the success of DCM. There is no regulatory precedent for DCM, and it will require a collaborative effort among technology suppliers, product manufacturers and regulators to establish a framework that enables DCM to succeed.

Concluding remarks and vision

The preeminent form of DCM was the franchise McDonald's. The man responsible for its success was Ray Kroc, and he recognized that consistency was the lynchpin to the success of the franchise model. Overcoming the challenges in site-to-site product consistency for French fries is much simpler than CGTs for two reasons: first, we can cheaply and reliably measure the

quality indicators of the "ideal" French fry; second, the governance and risk management of a food outlet are less stringent than that for a health care manufacturer and are able to be managed to acceptable standards with current technology.

The McDonalds French fry analogy does not aim to trivialize the challenges acceptance of DCM of CGTs face—they are anything but trivial—but rather demonstrate that two key barriers have a technological grounding and historically human ingenuity has readily overcome barriers that were purely technological in nature. We have outlined the substantial technological leaps made over the past decade and recognize that the ability to achieve consistency is getting closer each year as efforts to develop robust quality control procedures improves and our knowledge base increases [72]. Combining this technical advancement with the revolutionary effect the "IoT" and interconnected industrial systems are poised to have will facilitate product consistency and confidence across sites. Looking forward 10 years, we envisage a manufacturing paradigm that is undoubtedly different from historical trends; the extent of the adoption of decentralized business practices remains to be seen, but we remain confident that the supportive framework is emerging.

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