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# BioPharm INTERNATIONAL

March 2011

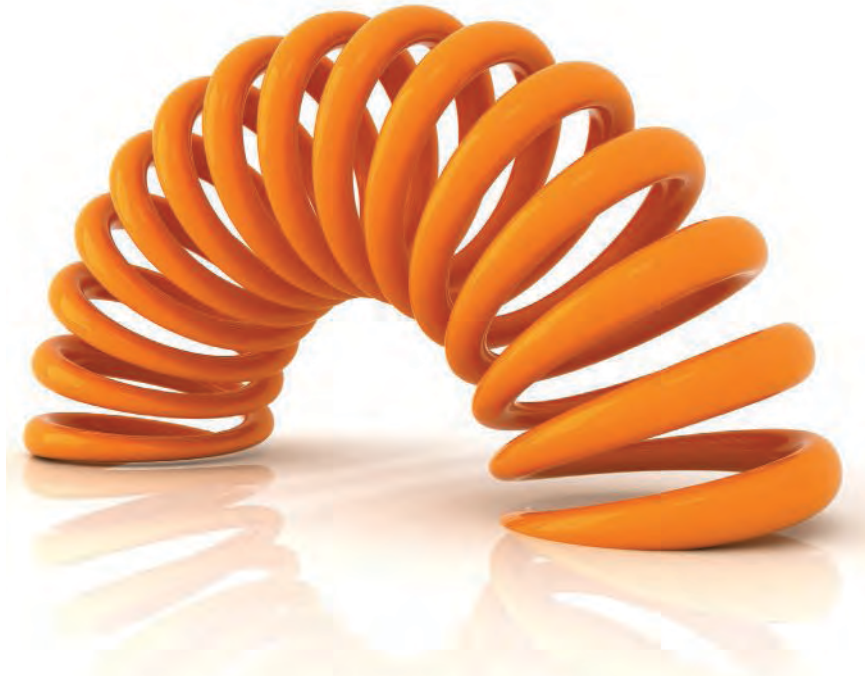
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Cover: Martin Barraud, Getty Images

# Sponsor–CMO Conflict Management for Clinical-Phase Biologics

Sponsor–CMO conflicts are best prevented before they emerge. Selecting the right CMO and negotiating the terms of the master service agreement are the first steps toward that goal.

NAPIERRE DOUETTE, PHILIPPE LEDENT, SOPHIE LEPAGE & PASCAL BOLON

## ABSTRACT

The long-term nature of outsourcing biologics process development and GMP manufacturing over the course of clinical trial development can involve unforeseeable events that could be a source of conflict between the sponsor and the CMO. In this article, we present the CMO's perspective on various potential sources of sponsor–CMO conflicts, preventive actions to circumvent conflicts before they occur, and strategies for resolving conflicts as related to process transfer, development, and GMP manufacturing of biologics.

A successfully outsourced GMP manufacturing program is built upon a common goal and the management of numerous factors in the complex collaboration between the sponsor and contract manufacturing organization (CMO). The successful collaboration involves a synergistic exchange of each party's knowledge and experience, combining detailed understanding of the product's intrinsic properties, experience in process development and manufacturing, and GMP regulatory requirements for manufacturing, toxicology, and clinical trials. In this article, the authors will present potential sources of sponsor–CMO conflicts, preventive actions to circumvent conflicts before they occur, and strategies for resolving conflicts as related to process transfer and development, and GMP manufacturing of bulk biologics.

## Conflict prevention in CMO selection

Numerous articles have already been published reviewing best practices in CMO selection (1–3). It is clear that the selection of a suitable CMO is

the first step in the prevention of conflicts. Mid-project changes in the service provider will only incur losses of time and money. As a rule, sponsor–CMO conflicts arise when a delivery gap is created in terms of product quality, quantity, cost, and timelines (see Figure 1). When the sponsor and the CMO first meet to discuss the potential partnership, it is important that the CMO not overpromise and that the sponsor not overexpect; aligning expectations is the first step toward minimizing a delivery gap. The interaction must be open, must highlight technical difficulties and pain points of the project, resource bottlenecks, and specify gaps in expertise of each party. A clear articulation of the project's scope, deliverables, and timelines should lead to the mutual acknowledgement of constraints related to the project. It should also bring about a mutual understanding of what the resources required to complete the project are.

At this stage, the CMO is responsible for accurately identifying the process steps that are incompatible with its existing facility or incompatible with the level of expertise required for the project. Doing so will ensure that the CMO avoids underperforming. For its part, the sponsor should have a total awareness of what is and is not known about the product to be developed and should be transparent about the state of development of the process, analytics, scales of previ-

PIERRE DOUETTE, PHD, is GMP quality control manager, PHILIPPE LEDENT, PHD, is process transfer and development manager, SOPHIE LEPAGE, PHD, is project manager, and PASCAL BOLON\*, PHD, is sales and marketing manager, all at Eurogentec, Rue du Bois Saint-Jean 5, B-4102, Seraing, Belgium, +32 4 366 61 16, p.bolon@eurogentec.com

ous runs, yields for each step, purpose of each process step, which process steps are problematic, and the behavior of the molecule during the process and under storage conditions. The desired quantities of material should be based on requirements for preclinical, clinical, future market needs, technical considerations, such as scale and process performance, characterization, and stability studies; the evaluation of these will require the intervention of both parties. Should incompatibilities exist, the two parties should brainstorm alternative approaches to meet the sponsor's expectations. This often has the added benefit of building trust between the two parties.

### Sources of conflicts following CMO selection

Assuming the appropriate CMO was selected on the basis of manufacturing capacity, process development, and GMP experience, and was followed by a compliance audit, the potential sources of conflict can be associated with the four broad steps in an outsourced project: business terms, technology transfer and development, project management, and compliance. An efficient contractual strategy can preemptively manage conflicts before they arise and can ensure that expectations, resources, and deliverables are understood mutually and can be allocated as required during project development (4–5). The specific needs of the project are often not definable before the project is initiated, so a contractual strategy that is both flexible and binding offers advantages over contrac-

tual approaches that attempt to cover the entire scope of the project, from development to GMP production, under a single technical agreement contract. Because the technical agreement cannot take into account all the eventualities of the project, it is inherently less flexible for the evolution of the project, and hence more likely to give rise to conflicts. A more flexible approach is to divide the contract into three distinct portions: the master service agreement (MSA), the project agreement (PA), and the quality agreement (QA). These agreements will reflect details outlined in the initial project quotation.

### Business-term tools Quotation

The quotation should not only serve as a starting point for the selection of an appropriate CMO, but should also be used subsequently as a reference map throughout the lifetime of an outsourced project. It should contain detailed information with respect to price, duration, start dates, development strategies, and deliverables based on the available information provided to the CMO. In the early phases of biologics process development and manufacturing projects, it is typical to define only the delivery date and estimated target amounts of GMP material. The sponsor then expects the CMO to offer a development strategy that meets the sponsor's deliverable requirements. As the development portion is variable from product to product, the quotation should be detailed enough for the sponsor to evaluate the CMO's proposal, and yet be flexible enough to provide pricing and timing

## An efficient contractual strategy can preemptively manage conflicts before they arise.

outlines that vary with the project's complexity. Quotations that offer this degree of transparency will help educate first-time, early-phase biopharmaceutical developers in terms of the time dependencies of various development steps. A Gantt chart can further highlight which steps are of variable duration (e.g., fermentation development), which are fixed in duration (e.g., GMP batch release), and what the time and cost requirements for each step to budget and plan. As a conflict-resolution tool, the quotation should provide sufficient information to allow a mutual understanding of pricing policy for additional work. For example, the quotation should include the cost and timelines associated with the transfer of a well-defined process as well as a per month, full-time-employee, or batch price for additional, optional optimization work, or other alternatives discussed at the point the CMO is chosen.

### Master service agreement

Discussions on the MSA should be initiated in parallel to the quotation. The purpose of an MSA is to lay out the legal contractual framework between the two parties, thereby allowing each party to protect their respective interests. The agreement should cover aspects that are not related to the techni-

cal deliverables of the project, including the legal responsibilities of each party with respect to the performance of service, data, reporting, material, intellectual property, licenses, third-party intellectual property, payment terms, warranties, duration, termination, confidentiality, insurance, indemnities, limitation of liabilities, and governing law. It should not include project details and quality matters, which will be respectively addressed in the PA and the QA. Separating contractual terms into these instruments allows the parties to put in place the terms in a stepwise fashion, designating the appropriate persons for each negotiation. The legal experts from both parties should agree on the legal clauses stated in the MSA, while the project managers independently move forward on the technical aspects of the project based on development results in a scientifically sound manner. This contract, once signed, initiates the start of the project as specified in the project agreements.

#### **Project agreements**

The PAs are annexes to the previously signed MSA and are an important conflict-management tool. The PA should describe the first project-specific tasks outsourced to the CMO by the sponsor. They are part of the legally binding contract. A project can have multiple PAs at the same time. For example, PA-1 can detail the transfer of a fermentation process, and PA-2 can detail GMP cell banking. Each PA should identify in detail the scope of the work to be done, which can be as comprehensive as required, including allocation of human resources, facility

resources, deliverables, delivery date, and price. Each PA acts as a yes–no decision point with respect to the general strategy agreed upon in the quotation. The outcome of one phase of the project will determine the scope of subsequent PAs. The content of the PA is often drafted by the various team members: the project manager, the scientists, and project leader, and the appropriate persons directly involved in development and GMP manufacturing. As a legal document, the PA is signed and approved by both the sponsor and CMO before work is begun. The significant advantage of a PA is to be able to define the phases of the project in a scientifically sound manner.

**The quotation should provide sufficient information to allow a mutual understanding of pricing policy for additional work.**

#### **Quality agreement**

The QA is a PA that covers GMP manufacturing of the product and is also annexed to the MSA. It should describe the respective roles and responsibilities related to quality and GMP regulations, and it should be outlined in a clear, straightforward manner. The sponsor's quality-assurance department or its representatives should ensure that quality aspects are properly managed in GMP drug manufacturing following a site audit of the CMO.

The QA should define the legal responsibilities of each party with respect to quality matters, such as manufacturing authorizations, audits, and inspections, facilities, staff and training, suppliers, third-party approval, raw materials, records and retention, product manufacture, storage, packaging and shipping, quality controls and out-of-specification management, change control and deviation management, complaints, and product recalls.

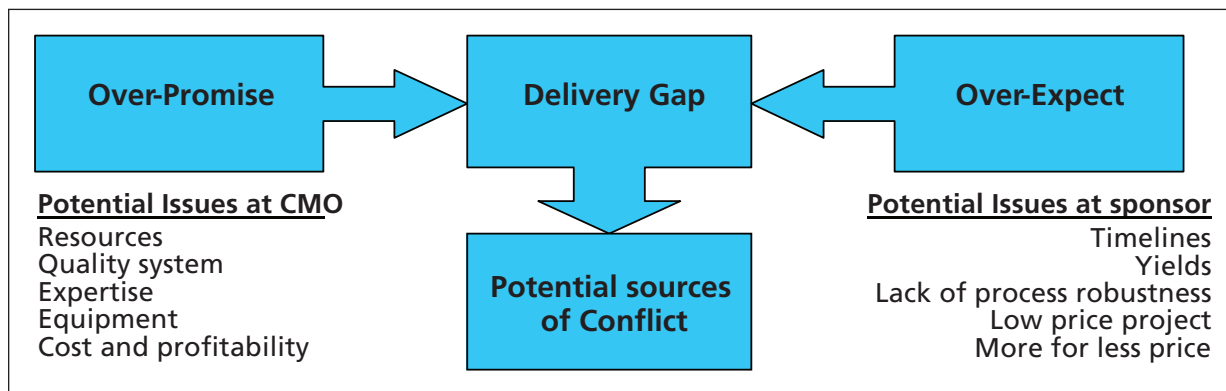
#### **Project go-live**

##### **Process transfer & development**

Once the MSA and PAs are completed, the sponsor and the CMO should agree on preventive actions before development and GMP manufacturing operations are begun. To avoid conflict during process development at an early stage of the project, the CMO should be irrefragable on the competency and expertise of its personnel, the equipment suitability, the quality of the reporting, and communication. Those in charge of development and GMP manufacturing should be aware of the PAs signed by both parties and should be of adequate expertise to lead process development and transfer to the GMP manufacturing facility. Second, the equipment in process development should be of the highest quality and should be comparable to GMP production equipment to ensure that transfer to the GMP production team is smooth and efficient. As a rule of thumb, the equipment should not represent a constraint that forces the CMO to come back to the sponsor with bad news.

Finally, during process development, the sponsor should be kept informed through frequent informal communication

**Figure 1.** Sponsor-CMO conflict management for clinical phrase biologics



and documented reporting. The frequency of teleconferences should be low enough to enable the CMO to ensure data reliability, yet high enough to ensure that the sponsor is sufficiently informed of ongoing progress: weekly communication is generally sufficient. Development reports should keep the sponsor apprised of key outcomes of the development stage and should reflect the scope of the different PAs. Finally, the CMO should share the sponsor’s priorities; its development experience should benefit the sponsor.

In spite of clear and careful agreements between the parties, the development stage can nevertheless be frustrating for both parties. Relevant expertise and technical mastery notwithstanding, there is no guarantee the CMO can provide deliverables and meet the sponsor’s expectations. It is likely that the parties will lose faith in the partnership. Conflicts that arise at this point are often related to people, time, financial resources, and the CMO’s scientific expertise. If a particular PA step does not satisfy the sponsor’s target expectations, the development

plan should be adapted with respect to the results of the initial PA in a scientifically sound manner. Because the plan entails process development, this adaptation may involve extra work and extra cost. In such situations, the following points are crucial:

- There are no questions with regard to the equipment, personnel expertise, and data generated
- Scientifically sound alternatives and their time and cost consequences are presented to the sponsor
- Authorization of a new PA is given by the sponsor before the CMO embarks on alternative development avenues
- The CMO acts with humility and acknowledges its limitations
- The sponsor acts in good faith and acknowledges the work is performed by the CMO, all the more when the product is difficult to handle or timelines are very aggressive.

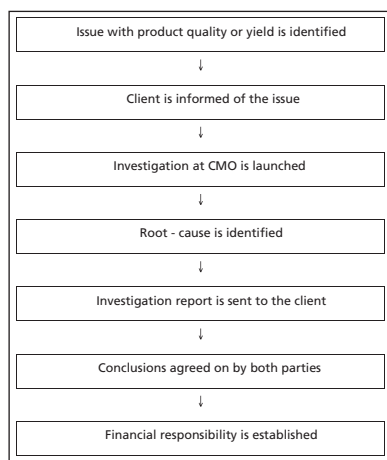
When advancing in a science-based manner, transparency in communication and detailed reports allow an accurate assessment of the work performed, even when development meets dead-ends.

**Risk assessments should be performed before initiating GMP manufacturing.**

**GMP manufacturing of clinical batches**

Risk assessments should be performed before initiating GMP manufacturing to ensure that product quality will be met. The CMO is responsible if it chooses to go ahead with GMP production when the risk of batch failure is high. Reasons for anticipated failure can include a lack of process robustness, insufficient process knowledge, and analytics’ undemonstrated fitness for purpose. At this point, additional development activities must be discussed to avoid overpromising. Finally, both parties should agree on the product specifications in accordance with regulatory requirements as well as the procedures and the method of production before starting GMP manufacturing. Target production yields and the customer’s needs to supply the clinic should be in good agreement with development data



**Figure 2.** Conflict resolution protocol

or process history upon normal operating conditions.

Following the risk assessment, the process is transferred to the GMP manufacturing facility. The technical transfer should never be jeopardized. The CMO is responsible for allocating all resources necessary so that the technology transfer is successfully achieved. The technology transfer should be documented, and the sponsor should be informed of the transfer's completion and any issues encountered. Likewise, the quality system in place must ensure the following points during the production of the GMP batches:

- The GMP personnel are adequately trained
- Equipment is qualified
- Operations are traced, recorded, and checked
- No cross-contamination occurs in a multiproduct facility.

### Conflict resolution in GMP manufacturing of clinical-phase biologics

Outsourcing biologics manufacturing is costly, and dealing with conflicts that involve financial arbitration is always

challenging. This statement is particularly true when GMP batch quality specifications are not met or production yields are not achieved (see Figure 2). Identifying financial responsibilities in these situations is often stressful and contentious. Senior management and appropriate decision-makers for both parties should immediately be informed of the issues and should take time reaching their conclusions following a thorough investigation. The investigation should be structured and systematically documented and should address the following technical and quality questions:

- Are the people trained in all affected operations?
- Is the equipment qualified?
- Are there any major or critical deviations in the method of production?
- Is the process robust or validated?
- Are critical steps identified or operating ranges well defined?
- Is the issue related to cleaning or cleaning validation?
- Are release specifications accurate with respect to product knowledge?
- Was an out-of-specification investigation opened by the quality-control laboratory?
- Is the out-of-specification root-cause assignable to a laboratory error?
- Are in-process controls as expected with respect to historical data?

This investigation should allow the development of a rationale for discussing the financial responsibility of both parties. In every case, successful conflict resolution depends on the quality of the investigation at the CMO and the sponsor's understand-

ing of the issue and root cause. Videoconference or face-to-face meetings are helpful in clarifying perceptions and promoting dialogue between the sponsor and the CMO. Generally, good conflict resolution, supported by facts and documented evidence, should benefit both parties and strengthen the partnership.

### Conclusion

Jointly building and documenting various tools before initiating a project will ensure that both parties are on the same page with respect to project goals. The use of a structured contractual framework based on a MSA, PAs, and QA provides the necessary flexibility to move process development and GMP manufacturing forward in a scientifically sound manner and under clear contractual terms in ways that a single technical agreement cannot. The reduced flexibility of a technical agreement can be a source of conflict. Although the MSA, PA, and QA are important conflict-resolution tools, successful projects benefit from collaboration, transparency with regard to capabilities and expectations, expertise, project status, and identification of specific subsequent milestones.

### Acknowledgments

We would like to acknowledge Ingrid Dheur, biologics director, and Florence Xhonneux, business development manager for their insightful comments. **BP**

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# Successful Technology Transfer, Process Validation, and Partnership with a CMO

The authors present lessons learned from a case study of the transfer of a cell culture biotherapeutic process to a CMO.

SUSHIL ABRAHAM AND HOWARD BLAND

## ABSTRACT

The use of contract manufacturing organizations (CMOs) for biopharmaceutical production offers many benefits, including deferred capital investment in building and validating a new facility for introducing new products to the market, bridging a technology gap, or as a second source of manufacturing for supply-risk mitigation.

The use of CMOs for production of biopharmaceuticals is fairly commonplace in industry today (1). This allows companies to accelerate the introduction of new products to market without the delay and cost incurred by having to build and validate a new facility. CMOs also provide an attractive dual sourcing strategy to mitigate product supply risks. Both the sponsor and CMO can reap benefits from this relationship if it is thoughtfully developed. However, the onus of oversight responsibility is clearly with the sponsor company as outlined in FDA guidance for industry (2).

This article looks at best practices for technology transfer (TT) based on lessons learned over the course of the TT of a cell culture biotherapeutic process to a CMO and the subsequent transition to commercial manufacturing operations. In this case study, the strategy for use of a CMO was to supplement existing internal production to meet expected product demand. The stages of TT shown in Figure 1 are outlined in the subsequent sections where the key aspects for a successful TT are discussed.

## Team formation, planning, and information transfer

Following the decision to use a CMO, the TT begins with team formation, planning, and information transfer. It is imperative to clearly define the scope and strategy for the TT. For example, if the objective is to demonstrate process and product comparability between an existing process and the one being transferred to the CMO, the strategy would be to minimize process and analytical changes to only those that are essential for fit within the CMO facility. Alternatively, if the objective is to improve process yield or throughput, there may be a greater tolerance for process changes. In forming the team, it is essential to clearly define roles and responsibilities of the sponsor and CMO teams. Figure 2 illustrates the team structure used to ensure that all aspects of the TT are considered. The TT core team brings together all work streams to ensure that they are aligned from a strategy perspective and highlight any issues that require cross-functional discussion and decision making. In addition to the core and sub-teams, it is important to have a governance structure for oversight of the TT and also to provide a forum

SUSHIL ABRAHAM\* is director of Process Development, and HOWARD BLAND is a director of Contract Manufacturing, both at Amgen, [sushila@amgen.com](mailto:sushila@amgen.com).

for issues to be escalated and resolved in a timely manner. Some of the key considerations during the team formation phase are as follows:

- Ensure that teams have effective tools for communicating between sites (e.g., web-based teleconferences, a web-based server for storing and sharing information). Details such as meeting frequency and expectations for communication between teams should be clearly outlined at the start.

- Ensure that team accountability is clearly defined. It is important to have a good mix of technical and business and project management support, which enables clear focus on core competencies. This allows the TT lead to focus on ensuring technical success while the business or project manager can focus on the framework and financial aspects to ensure overall TT success.

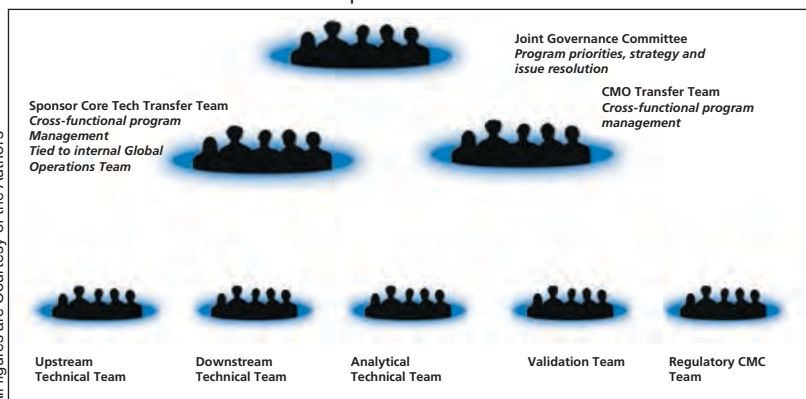
- Ensure direct, face-to-face contact; for example, during project kick-off and milestone reviews. In these days of greater economic stringency, this is an area that is often the first to be cut to help reduce project costs. However, we would recommend that this is seen as a 'must have' for ensuring success of the TT.

- Training for teams on cultural nuances and work styles when dealing with international transfers. Awareness of differences in corporate and regional attitudes to work are important to ensure that teams can achieve their common goal of a successful TT. For example, some companies and cultures tend to have a more hierarchical approach while others tend to have a more direct engagement style. There is no right

**Figure 1.** Stages of Technology Transfer.



**Figure 2.** Team structure for technology transfer encompasses strategic and tactical execution. The various technical teams shown are joint teams and include members from both the sponsor and CMO.



or wrong in this regard. What is essential is that teams have awareness and respect the other's style and that, as a combined team, they find an effective middle ground.

- Training by the sponsor company for the CMO on their product-commercialization program so that expectations are clear from the start. There should be dialogue during this stage to ensure that CMO policies and practices will meet the sponsor company's quality and business expectations.

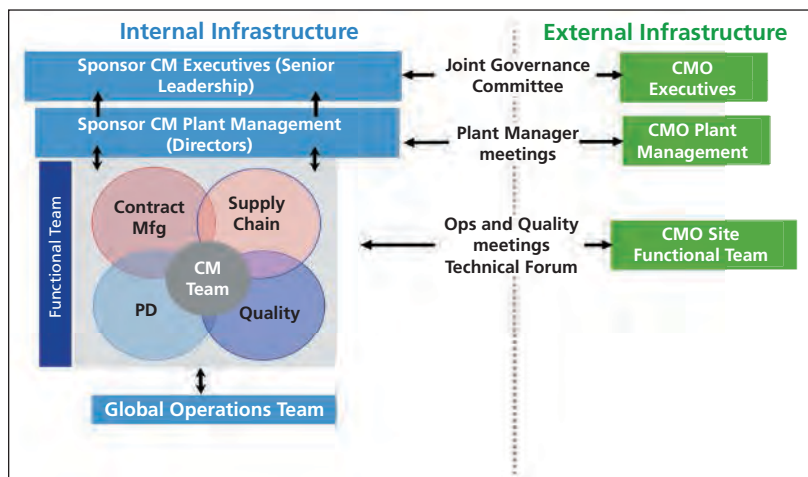
- The working team should be encouraged and empowered to try and work through issues as much as possible and within budgetary accountability. It is important to find the balance between empowering the TT team to make decisions versus escalating everything to the governance team as the latter could become overly cumbersome and result in delays to the TT timeline.

- Be mindful of changes in the key members of the TT

team, especially for leadership roles. Ideally, once the TT team has been assembled, it is important to maintain continuity in the team through TT to maintain knowledge and momentum. This also allows a solid relationship to form between the sponsor and CMO.

In the planning phase, the work plan forms a key document to list the key goals, assumptions, activities, deliverables, project timelines, and key milestone expectations. The work plan is a legally binding document used in conjunction with Quality and Supply Agreements so that the sponsor and CMO have clarity on expectations for the project moving forward. Defining a team charter and roles and responsibilities document as a joint effort is useful in ensuring clarity and avoiding issues later in the project. In our experience, it is rare that a complex TT project would have all the right assumptions from the start. It is important that the

**Figure 3.** Transition to site management model during transfer to commercial manufacturing.



CM is contract manufacturing; PD is process development; and GOT is Global Operations Team with an overall product focus.

teams be adept in their ability to foresee the need for changes and assemble data justifying the change required. The scope and cost of the change should be defined and reviewed with the governance team for approval so that the project can keep moving forward without delay. Key through all stages of the TT is the need to avoid revisiting decisions once they have been made. It is important to document the decisions made, assumptions at the time, identified risks, and the agreed-upon path forward.

The information transfer stage involves the exchange of a large number of technical reports detailing the process and analytical methods. However, it is essential that this is not just seen as the exchange of documentation. While the coordinated transfer of documentation is an essential part of TT, the availability of CMO staff to observe the process as operated at the sending site (manufacturing, pilot, and laboratory

scale) is essential in ensuring that the nuances that may not be captured in the documentation are also identified and discussed. As mentioned below, face-to-face meetings provide the best forum for active discussion of potential issues and changes that may have to be made to facilitate the process fit within the facility.

It is also important to stress that the information transfer is not a one-way affair from sponsor to CMO. The CMO needs to provide relevant equipment and facility information and also provide documentation to ensure that they have correctly understood the process. This type of dialogue and information sharing is sometimes constrained under the guise of what is considered proprietary information so the confidentiality aspects should be appropriately covered in the contractual agreements to ensure that both sponsor and CMO are able to share necessary information. It is important that the teams not

make poor assumptions that would otherwise be identified later during engineering or validation runs with serious consequences to the project success and timelines.

### New Product Introduction (NPI) phase

During the NPI phase, the process is operated at the CMO prior to the formal validation campaign. Some CMOs have developed scaled-down laboratory and pilot models that allow them to gain familiarity with the process without tying up valuable commercial manufacturing facilities, which would add to project duration and cost to the sponsor. This allows the consistency and robustness of the process to be evaluated by the CMO at an early stage in the transfer. Process changes for facility fit purposes may be evaluated during this phase. Additionally, the availability of qualified scale-down models is vital for effective troubleshooting in manufacturing. Typically, if the sponsor company is leading process characterization, it would be responsible for evaluating and performing supplemental process characterization studies to confirm the impact of any required process changes to the product and process. However, this should be discussed, and the tech-transfer team should distribute workload between sending and receiving teams to best use technical expertise and effectively maintain project timelines. The laboratory and pilot runs allow an opportunity for testing the raw materials to be used in the process. Risk assessments based on historical knowledge may help classify

raw materials as crucial, where sponsor and CMO must agree on the supplier, and non-crucial where the CMO may use an alternative vendor with similar specifications. However, it is important to stress that this should be tested at laboratory and pilot scales to confirm that the final raw materials selected do not have any impact on the process and product quality. Experiences from the laboratory- and pilot-scale studies as well as supplemental process characterization help to drive the scope for the next stage of the NPI at the commercial scale.

At the commercial manufacturing scale, automation-, wet-testing, and engineering runs should be executed prior to the validation campaign. These are performed under development protocols so there is clarity on the goals and success criteria as well as the methodology to be used. At this stage of the program a balance needs to be reached between desired engineering run rate that provides time for data analysis and adjustment between runs, available facility time, and campaign cost. The engineering runs (sometimes referred to as shake-down or test runs) are product runs performed as a means to ensure that the process performs as expected before commencing the process validation campaign. Key considerations for this stage are as follows:

- Should the engineering runs be done to GMP or non-GMP standards? The latter offers greater flexibility in making modifications to the process under the guidance of technical experts without being constrained by the GMP requirements for change con-

trol and batch-record approval. However, the material from this non-GMP engineering batch cannot be released for clinical or commercial use. Another consideration is with respect to use of raw materials, such as chromatography resins from the engineering to validation campaign. The high cost of the resin makes reuse attractive between campaigns. The requirements for allowing resin reuse should be outlined in a protocol. Following execution, the data should be summarized in a report confirming that the resin is fit for use in validation runs.

- The number and stagger between runs to allow evaluation of process data and any process or equipment modifications to be made. Conducting runs back to back leaves little time to identify a problem, investigate its root cause, and develop potential corrective action, so that the problem may affect multiple runs. This requires careful balancing of technical risks and the cost of running at a slower pace to allow for such process troubleshooting.

- Availability of scale-down models to run the process concurrently and aid with potential trouble-shooting work.

- Ensuring that contingency plans are developed for high or medium risk issues identified during the information transfer and pilot-scale studies. This allows one to react quickly to potential technical problems that may arise during the execution of the engineering runs. Contingency plans should consider additional runs to confirm that corrective actions remediate any problems identified.

## Clarity in communicating one's expectations is the key to successful sponsor/CMO relationships.

- On-site presence of technical experts from the sponsor company to ensure that the process is operated as originally designed and to aid in process troubleshooting. This also helps to ensure fast communication back to the sponsor company so there is transparency in operations.

The engineering campaign tends to be the most intensive phase of the TT. A readiness assessment is a key output from the engineering campaign to ensure that the process is operating as expected and that all issues identified during the campaign have been adequately addressed such that the team is ready to move forward to perform process validation.

### Process validation

The culmination of the TT work is the execution of the process validation campaign. There may be differences in validation strategy between the sponsor and CMO, so early initiation of discussions between validation experts at both companies is recommended. The output of these discussions is documented in the Process Validation Master Plan (PVMP), and process validation study protocols. In addition to these, it is recommended that a process validation support plan is defined. The support plan

details roles and responsibilities during the validation campaign, ensures that data are actively being monitored and verified so that issues can be identified and resolved rapidly without affecting the overall validation campaign. Both parties should agree at the beginning about how frequently they will meet to review performance parameter (process outputs) and operating parameter (process inputs) data. On-site presence from the sponsor company especially for critical steps in the process is recommended during the validation campaign. This also facilitates discussion to identify any parameters excursions to understand impact on the integrity of the validation study and if any additional runs are required.

### **Regulatory filing and preapproval inspection (PAI)**

Following completion of the validation campaign, the data from the validation campaign are consolidated in process validation study reports. Sufficient time should be allowed to draft and review the Controls, Manufacturing, and Chemistry (CMC) sections of the regulatory dossier. The roles and timelines to write and review CMC sections should be clearly defined. It is necessary to ensure that the CMO is aware of timelines for responding to questions from regulatory agencies and that resources are made available for this activity. A clear communication plan is crucial to ensure that regulatory questions are answered by the appropriate individuals within a specified time. It is important to prepare

early for the PAI so that problems are corrected before they delay approvals and licensure. Sponsors should consider performing mock audits and sending their subject matter experts and quality management on-site for the PAI.

### **Transition to commercial manufacturing**

During the transfer to commercial manufacturing operations, it may be necessary to make some adjustments to the team structure and level of engagement. One organizational approach that we have found to be effective is to have a virtual site-management structure as outlined in Figure 3. This consolidates the various subteams that were engaged during the TT into a more sustainable format. The core team is more operational and quality focused to ensure continued success in delivering product to target metrics for quality, speed, and cost. Oversight *via* a governance team is still maintained.

From a technical aspect, an important consideration for the transfer to commercial manufacturing is to finalize plans for process monitoring. The parties should share and document their expectations about which in-process controls will be monitored as well as the methodology for establishing statistical process control (SPC) limits and identifying process shifts and trends. They should also agree on how this information should link to quality systems for deviations, change control, and annual product reviews. It is also important for the parties to agree on the frequency of data review, and how the team responds to SPC signals so that

appropriate corrective action is taken where necessary.

### **Conclusion**

Key to successful TT and a mutual beneficial relationship between sponsor and CMO is clarity in communicating expectations. Clearly aligned objectives and deliverables and well-defined roles, responsibilities, and team structure from the onset will lay the foundation for a successful working relationship. There should be appropriate oversight and governance structures in place. Teams should be mindful of cultural and corporate nuances and use appropriate communication tools, including face-to-face meetings for milestone project reviews and to build a cohesive team. The need to periodically assess TT and operational risks and develop contingency plans helps to mitigate such risks. The level of engagement would be expected to evolve depending on the operational phase, for example, during the transition from TT to commercial manufacturing. Underlying all of this is a relationship that is built on trust, which improves the speed and cost of doing business and maximizes benefit for both sponsor and CMO.

### **Acknowledgments**

The authors wish to thank Ali Siahpush and Jian Irish for their insightful comments and guidance in preparation of this manuscript. **BP**

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## Key Considerations When Outsourcing Cell-Culture Medium Development

The authors examine several issues that will help streamline negotiations between a service provider and a cell-culture medium consumer that plans to develop a cell-culture medium.

TRENT CARRIER, STEVE GORFIEN, AND BRIAN GRIFFITH

**T**he rational design of cell-culture medium originated with Harry Eagle in 1955 when he began culturing cells in what would eventually become the progenitor of Eagles Medium (1). In subsequent decades, suppliers established a commercial market for the development and supply of cell-culture media. Over the next 45 years, these suppliers brought significant innovation to this field, including introducing the first serum-free medium, pioneering the creation of new media formats, and enabling many of the current high titer cell-culture processes. As the value of products derived from mammalian cells exponentially increased, so too has the

demand for medium to culture cells. Today, cell-culture media for biological manufacturing represents a sizable market of more than \$500 million, but more impressive is the cumulative value of therapeutic products enabled by these reagents, which totals more than \$35 billion (2). Given the importance of these reagents, major suppliers, drug manufacturers, and other biotech companies continue to make significant investments to improve their cell-culture media platforms. Despite the

TRENT CARRIER is General Manager of PD-Direct Services, STEVE GORFIEN is an R&D Director—Cell Culture Products and Services, and BRIAN GRIFFITH is Division Contracts Counsel, all at Life Technologies, Trent. Carrier@lifetech.com.

**Figure 1.** Commercial scale-up considerations should be part of any custom medium development.



**Figure 2.** A knowledgeable medium-development partner will help sponsors identify and set goals and priorities.



tremendous value created by cell-culture media and the investment poured into research and development, this field remains a rather immature territory for efficient outsourcing models.

This article addresses some of the key issues that a company needs to think about when deciding to outsource development of a cell-cul-

ture medium. An outsourcing partner who understands these issues can provide guidance that will allow for informed choices about the sponsor's project goals.

#### **Clearly defined technical goals**

The first place to start when considering outsourcing is the technical goals of the project. Project

expectations can vary widely, even among members of the same team; therefore such expectations need to be fully vetted, and priorities need to be set during the preliminary outsourcing discussions. The specified goals will ultimately define the technical approach for the project. While multiple goals can be designed into a project, budget and time constraints likely will force both parties to set priorities.

For example, a project goal might be to improve process consistency by removing undefined components (e.g., hydrolysates) from the production medium (3). If this is the case, then targeting productivity improvements should also be considered as a separate development initiative because a developer would likely use a different technical strategy for eliminating hydrolysates than they would follow for improving cell productivity. In fact, these two particular goals can appear to be competing if a cell-culture medium is not properly balanced (4). Likewise, a development project aiming to optimize a medium for a specific clone will look significantly different from a project where the primary technical goal is to develop a platform medium that works across multiple products and multiple clones. In the latter case, a developer is often faced with selecting criteria that work best across multiple clones at the sacrifice of performance of any single clone.

Finally, within the technical scoping of the project it is important that the medium developed can ultimately be manufactured at a scale and in a format that will support commercial production (see Figure 1). Beyond production considerations, the developed medium will also become part of your chemistry, manufacturing, and controls (CMC) regulatory submission. It is therefore essential

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to have the requisite quality controls (i.e., process validation, release specifications, stability, and shipping robustness) to fulfill regulatory filing requirements. This final aspect of technical scoping is often overlooked by research scientists; however, a medium-development partner should frame these considerations to fit within the sponsor's overall technical strategy.

In defining the overall technical goals, it is important to understand the starting point for development, not only in terms of the medium one is starting with, but also in terms of the quality of the cell line and the expected yield. Regarding the medium, the goals one sets for optimizing an in-house medium that one has worked with for several years will likely be much more specific compared with a vendor's catalog product that has been minimally optimized. Likewise, the technical approach for a robust cell line with expected high yields will not be the same as a project designed to salvage a low-producing cell line where any improvement will be welcomed. The factors described above relating to the medium starting point and the quality of the cells (as well as the expected yield) will determine how substantial a development effort is needed (and therefore the time and cost of the program).

### Well-defined project structure

While scoping the technical aspects of a project to develop cell-culture medium, one needs to outline the project structure in parallel. Within the project structure, one needs to determine the amount of laboratory work that will be performed in-house versus outsourced, identify any critical performance steps that need end-user verification, and agree upon norms for joint team decisions. Also to be considered

**Figure 3a.** Life Technologies's media-manufacturing site in Grand Island, New York.



**Figure 3b.** Life Technologies's media-manufacturing site in Inchinnan, Scotland.



is whether the project has a time-critical element (such as the need for Phase II manufacturing in six months), as the technical strategy will be affected by how much experimental time can be dedicated to the project. For example, the sponsor may choose a sequential two-level study design followed by a central composite design of experiments (DOE) to pick the optimal medium formulation if the project can extend to 10–11 months; however if the sponsor has only three months, the project would more likely be designed following a single integrated basal medium or feed study to improve performance

beyond current baseline (5). In each of these examples, having a knowledgeable media-development partner will allow the parties to set goals and priorities (see Figure 2).

Beyond project specific decisions, performing the appropriate due diligence on a potential outsourcing partner's business processes is crucial. In particular, sponsors should inquire about success rates, functional roles within the project team, program management, and how the service provider manages crucial project decisions. Such "outsourcing best practices" are beyond the scope of this article, but are discussed in depth by several other authors (see,

for example, the article by Douette et al. in this supplement). Most authors on this topic agree that a strong program-management infrastructure and proven track record are essential to minimizing the risks of outsourcing process development (6).

### Medium supply terms

Thinking about medium-supply terms at the outset of a medium-development project might seem premature, but addressing certain concepts at this phase will make the overall process smoother. A medium-development partner that has thought through supply issues, and preferably has an established plan for commercial medium supply, will have a long-term advantage as the project proceeds. One difficulty in addressing supply terms at the outset of a medium-development project is that since the final product does not yet exist (because the medium is still to be developed), any terms should be flexible enough to handle unexpected outcomes or changes in the overall project scope or design. In most cases, a supply agreement should include pricing tiers by volume based on annual forecasting and a common set of quality standards. In recent years, as the biopharmaceutical industry has become more focused on risk management, many companies have begun to seek additional safeguards against an extended interruption in culture media supply. Most suppliers will present redundancies within their manufacturing operations as an assurance of continuity of supply (see Figure 3a and 3b), and direct any additional safeguards to be outlined within a supply agreement. In general, it is a good strategy to ensure that the general supply concepts are covered and save the final details until the development program is complete.

### Intellectual property ownership

“Lifting the veil of secrecy.” “Breaking the code.” Such phrases may sound like a plot for a 1920s movie, but in fact these expressions describe a challenge faced by every cell-culture scientist charged with improving bioreactor productivity while being blinded to the composition of the medium used to culture the cells. Historically, improvements in medium performance were primarily reimbursed to developers through profits on media sales, which led vendors to maintain successful innovations as trade secrets to recoup their R&D investment.

Despite this history, visibility to the composition of cell-culture media formulations is becoming a priority as the field becomes further specialized and therapeutic companies become more focused on product life-cycle management. As a result, the parties should discuss the level of knowledge-sharing about the composition of custom media in any outsourcing negotiation. Typically a project sponsor will desire disclosure of a medium formulation for regulatory and further internal development purposes, while the developer will be concerned about protecting intellectual property and freedom to operate. One standard approach is for the developer to maintain ownership of the medium formulation and contractually define end-user rights to the intellectual property. Often, such intellectual-property terms can be linked with supply-agreement terms that address everyone’s business interests. Experienced outsource providers will have thoroughly thought through these issues and can offer helpful guidance on what is best practice as it relates to a specific project.

### Conclusion

Although not a comprehensive listing, the areas discussed in this article are four of the most important issues that will help to streamline the negotiations between a service provider and a project sponsor interested in partnering on the development of a cell-culture medium. As the technology platforms continue to push new boundaries, we will need to continue to look for new ways to realize and share the value of those discoveries. The collective lesson for our industry has been that technical innovations in products and services must be matched with business innovation to continue to best serve patients.

It is clear that striking a balanced approach to the outsourcing discussion is crucial for achieving the project goals. An imbalance in any of the four areas discussed will set the outsourcing relationship on the course to disappointment; however, if done properly, a progressive philosophy on sharing risks and benefits will turn an arm’s-length outsourcing relationship into a productive collaboration.

### Acknowledgments

The authors wish to thank Cindy Goldstein and Laurie Donahue-Hjelle for their editorial contributions to this article. **BP**

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## Supply-Chain Transformation: Strategic Necessity for the Life Sciences

New supply-chain challenges, including counterfeits, are forcing companies to act in different ways to secure product safety.

CARLA REED

**F**ueled by the discovery and commercialization of blockbuster drugs, life-sciences companies have for decades enjoyed profitability and growth. Seemingly immune to the challenges faced by other industries, including the clothing and apparel, electronics, and automotive industries, companies in the life sciences have enjoyed ongoing investment, enabling the formation of new entities in the evolving biotech sector.

These halcyon days for the life-sciences industry are over. The combination of the expiration of patents for high-revenue products, failure of products within the discovery pipeline, and the global economic decline has cast a cloud of doom. Mergers, acquisitions, and consolida-

CARLA REED is a principal at Tunnell Consulting, Inc., tel. 610.337.0820, reedc@tunnellconsulting.com.

tion are symptomatic of these issues and have created challenges for stakeholders and constituents, not the least of which is the pressure to reduce cost, improve cash performance, and either consolidate facilities or outsource manufacturing and other functional areas. Emerging economies in the BRIC nations (Brazil, Russia, India, and China) as well as their satellite “factory states,” are harvesting the benefits of this shift in operational focus, with industrial areas mushrooming up seemingly overnight to provide factories and human resources to meet the growing demand for so-called offshore manufacturing. Recognition of the importance of mastering a global network of operations, many components of which are now run by external parties through an ongoing trend to outsource perceived noncore functions, has placed a spotlight on the teams and leaders responsible for delivering quality products and services.

### **New business models elevate supply chain**

As sources of supply and demand change, so must business strategies for the manufacture and distribution of life-science products. Supply-chain management, once considered a mere support function, is a crucial component of today’s outsourcing environment. Executive suites have opened their doors to the focus, and many leadership teams now focus on supply-chain issues.

During the past decade, leading global companies have recognized the importance of supply-chain management, creating cross-functional teams

to integrate their supply and demand operations. There are many examples within the electronics industry of companies that have created collaborative supply-chain environments facilitated by the combination of industry best practices at the process level and powered by information technology. Building on the foundation of “inter-enterprise” collaboration, facilitated by the adoption of a single technology platform (e.g., large scale enterprise resource planning systems), this model has been extended to include external players, delivering on the promise of the extended virtual enterprise.

Until now, buffered from the economic necessity to take such actions, life-sciences companies have been slow to follow. The increased requirement to reduce cost, complexity, and risk, however, has created a compelling case for collaboration across the global network of suppliers and third-party logistics providers and customers. Many companies are taking advantage of the capabilities of new partners—contract manufacturing provides a good option as new products find their way to market—especially in emerging economies. Outsourced relationship models should build upon the regional knowledge of the contract manufacturing or logistics providers to create a sustainable supply-chain network to meet current and evolving needs.

### **The fine balance between supply and demand**

In common with big pharmaceutical companies, biopharmaceutical companies are reevaluating their supply

## **Companies are creating cross-functional teams to integrate their supply and demand operations.**

chains and looking at outsourcing and contract manufacturing as a growth strategy. However, unlike traditional pharmaceutical companies, who are currently focusing on reducing costs, biopharmaceutical companies are more concerned about managing the risk factors that have been introduced throughout their extended supply chains. This difference was evident during presentations and panel discussions at the Biotech Supply Chain Academy event held in San Francisco, in October 2010. Concerns related to supply disruptions, particularly for single- or sole-source suppliers, were common. The impact of a shortage, or worse, contamination, of a key ingredient that could prevent manufacture of crucial compounds was a major concern. Whether considered from the viewpoint of financial loss, reputational risk, or patient safety, supply disruptions are a major challenge for biopharmaceutical companies. As products move from discovery to commercialization, stabilizing supplier relationships is crucial, but complicated. Projecting demand for new compounds requires close communication between man-

ufacturers and healthcare professionals.

An additional factor for consideration is an increasing focus on the patient, in many cases requiring specialized supply-chain management and oversight from manufacturing location to the end user. Because some biotechnology products are designed and developed to address issues for small patient communities, the sector has facilitated an environment of patient intimacy, with close cooperation between companies, caregivers, and beneficiaries. This advantage should be incorporated into supply-chain strategies.

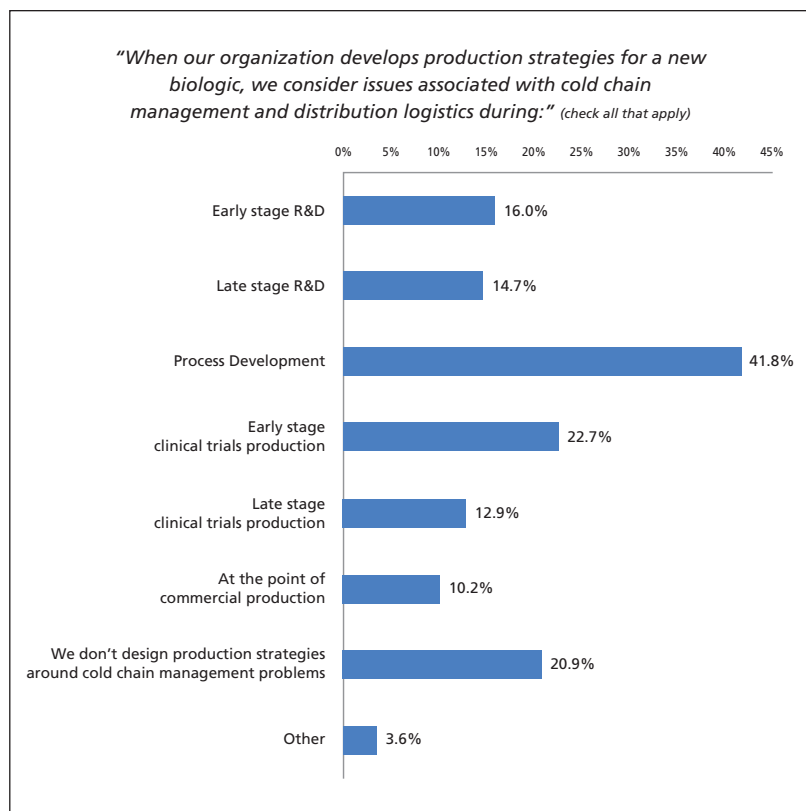
### Additional risk factors for biotech companies

In the case of biotechnology products, the stability of the ingredients and components is a crucial element and one that needs to be managed across the product life cycle, from acquisition and transformation to distribution and consumption.

Cold-chain management is a key factor for nearly all biotechnology products. However, this challenge is not always taken into account during the transition from discovery and product approval to the commercial-manufacturing stage. Figure 1 reflects responses on this topic from the Sixth Annual Report and Survey of Biopharmaceutical Manufacturing, conducted by BioPlan Associates in 2009.

According to Eric Langer, president of BioPlan Associates, "Cold chain management of biologics is becoming an increasingly important function in the overall marketing, manufacturing, and produc-

**Figure 1.** Respondents indicate the phase of process development during which they first consider cold-chain management (Data reprinted with permission from the *Sixth Annual Report and Survey of Biopharmaceutical Manufacturing*, BioPlan Associates, 2009).



tion of these products. If the infrastructure for delivering these products to end-users is not available, or is inadequately controlled, product quality and drug efficacy may be compromised. As global markets for biologicals expand, this has become an increasingly important issue."

### Counterfeiting and diversion

Counterfeit drugs are a growing global problem, one that the biotech industry shares with other sectors in the life sciences. While some of the most troublesome cases involving counterfeit drugs have flowed through traditional drug distribution channels, globaliza-

tion of drug manufacturing techniques and direct-to-consumer product delivery *via* the Internet, mail, and direct-to-door carriers have formed new distribution channels for counterfeit drugs. Other issues include increased production of counterfeit pharmaceuticals and biotechnology products in locations that are sources of supply for legitimate products, such as China.

The introduction of counterfeit or diverted biotechnology products into legitimate channels is a real threat that requires oversight from brand owners and their supply chain partners. The impact of counterfeit drugs is felt across the

whole supply chain—at times with fatal outcomes. There are a number of mechanisms and techniques either in use or in development and design to ensure that the biotech product is authentic and to combat counterfeiting. This includes a drug pedigree or, in conformance with pending California legislation, an ePedigree. (An ePedigree is an electronic record containing the information regarding each transaction resulting in the change of ownership of a prescription drug from the manufacturer through distribution to the dispensing of an individual unit of a drug by a pharmacy or hospital. Companies are required by FDA to maintain pedigree reports and must be prepared to have them audited.) With proper implementation and controls, the chain of custody for a pedigree document can be established, creating a high degree of confidence in the origins and authenticity of an item.

### Forging the links across the chain of custody

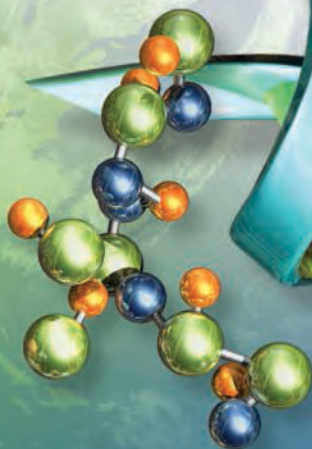
Short product life cycles—that is, compounds and components that are susceptible to variations in temperature, vibration, and environmental factors—create challenges for all participants in the biotech supply-chain community. Visibility across the chain of custody in an increasingly global network has become a necessity.

When addressing the challenges of global logistics, with additional complexity of regulatory compliance, one should take into account both sources of demand and supply, providing additional oversight in the chain of custody. Product protection through specialized packaging and information technology components, including temperature sensors, monitors, and auto-identification tools, should be introduced to ensure that delicate life-saving compounds are not compromised on the path from production to patient. Standards, policies, procedures, and processes to safeguard the security of the supply chain should be agreed to by all participants (no matter how small their role) and should be reinforced by clearly defined service level agreements and reporting mechanisms. With all company participants focused on the same goal of delivering a better quality of life to patients, true supply-chain transformation is possible. **BP**

## Guiding principles for supply chain management.

- 1. Educate the chain:**
  - It is crucial that all supply chain partners are aware of their role in ensuring safety and compliance
  - Service level agreements that are part of the legal terms and conditions of procurement and service contracts should be used to help ensure compliance
- 2. Demand data collection excellence:**
  - In many cases, the technical capabilities of suppliers—or lack of it—can create constraints
  - Parties should understand and plan for data collection, capturing required data elements and required information through media in place and digitizing this as soon as possible
- 3. Institute documentation and communication consistency:**
  - Documentation is crucial to ensure that the correct packaging, storage, and handling procedures are consistently applied
  - Communicate and share information with all participants in the chain of custody, taking into account language, literacy and other constraints
- 4. Pay full attention to recall and destruction:**
  - It is all-important to ensure that members of the extended supply chain know what to do if the product has been compromised and spoiled
  - This should be clearly outlined in service level agreements between all players in the pharmaceutical supply chain
- 5. Be obsessive in continuous monitoring:**
  - Take nothing for granted. Insist on timely and accurate records for product recall, processing, and destruction
  - Outsourcing is no excuse for negligence
  - Best practice companies put in place data analysis processes and human knowledge collection procedures to spot specific red flags in their end-to-end supply chains
  - Changes in cost elements, participants, trade lanes, and modes of transport should be investigated.

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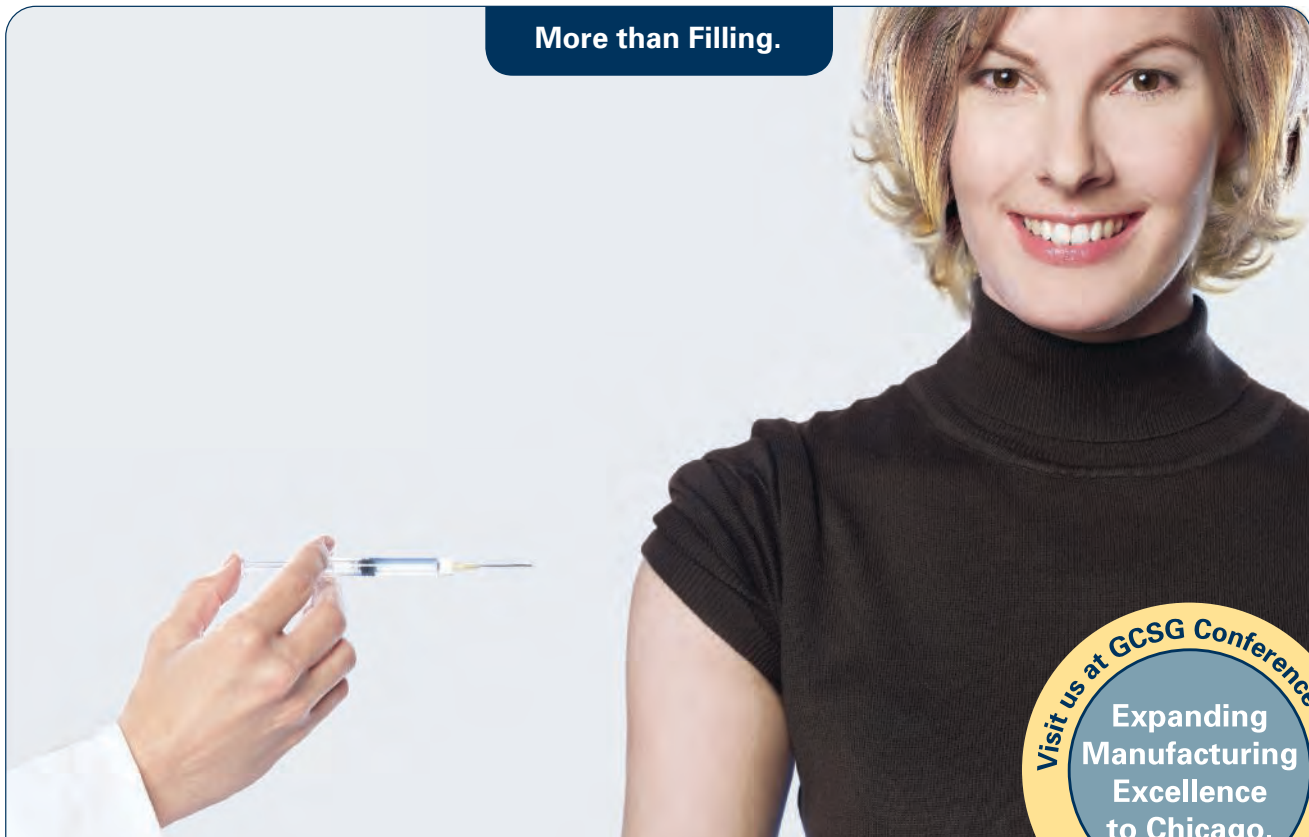
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