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## Third Party Due Diligence

Due diligence is an investigative process for validating representations made by one party to another. Due diligence is typically performed before two companies enter into a significant commercial agreement, for example a merger/acquisition, a technology license, or a joint venture. A detailed due diligence process typically begins after initial interest between the parties has been established but prior to signing binding contracts (other than confidentiality agreements).

When the companies are competitors, they are often reluctant to engage in due diligence because of a fear of “cross-contamination” occurring, or the appearance of such. Cross contamination refers to one company acquiring critical know-how from the other company during the investigative process. To avoid cross-contamination, a third party is often brought in to perform the due diligence and act as a “firewall” between the two companies.

For example, because of our expertise in drug delivery technologies, IMPACT was recently engaged by a large foreign pharmaceutical company to perform third party technical due diligence of a small drug delivery company. Both companies are developing sustained release drug delivery platforms. Based on encouraging feasibility study results, the large company is considering licensing technology from the smaller company, and engaging in a joint development project. The large company sought an assurance that the data presented by the small company were valid, an assessment of the scalability of the drug delivery platform and manufacturing process, and an evaluation of the small company's ability to manufacture aseptically under cGMP.

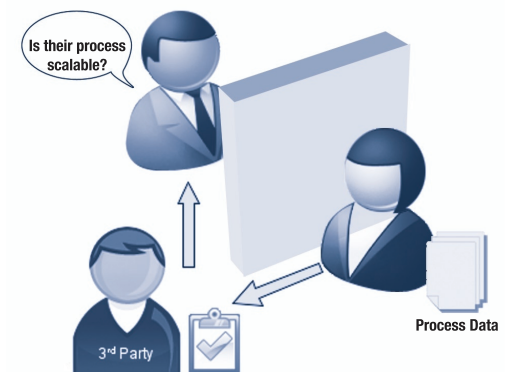
The timeline was very short, and the consequences of a mistake were high. IMPACT's fast-track technical due diligence approach was followed. The key steps in this approach are:

1. Provide a clear set of objectives to all parties in advance
2. Send an advance list of questions
3. Perform three or more pre-visit telephone conference calls. The calls address the following: scope, relationship building, timeline establishment, and preliminary Q&A.

4. Perform a site visit to perform a detailed review of batch records and lab notebooks and to interview operating, scientific, QA, and regulatory staff. The purpose of this visit is to validate the answers to the list of questions by reviewing primary records, to ask follow-on questions, and to perform a site inspection. One to two IMPACT team members will perform the site visit.
5. Perform a post-visit follow-up conference call with additional questions.
6. Prepare a draft report.
7. Provide a copy of the report to the audited party for review of potentially confidential information and to provide an opportunity for them to dispute or clarify the factual basis of findings.
8. Submit a final report to client.

Following this procedure, IMPACT was able to efficiently, quickly, and thoroughly assess the capabilities of the smaller company and provide a thorough report to our client within three weeks. While the smaller company may not have agreed with all of our conclusions, they were able to ensure that we did not disclose confidential information and that our supporting facts were correct.

The key to the success of this third party due diligence was choosing a partner with the specific technical expertise in the field to maximize the efficiency of the audit and ensure that the analysis was thorough, detailed, and accurate.



Third Party Due Diligence maintains a “firewall” between two companies with potentially overlapping technologies.

## TECHNOLOGY HIGHLIGHT: CARR® Process Centrifuges

Process centrifugation technologies can be characterized by the following parameters:

- **Design:** tubular bowls, chamber bowls, disc stacks, solid bowls, filtering, etc.)
- **Operation:** continuous, semi-continuous, or batch
- **Scale:** bench, pilot, or commercial

Process centrifuges can also be segmented by application, which naturally results from the particular strengths and capabilities of each technology being best matched with a given set of process requirements.

When considering process centrifugation during process development, scalability is a critical factor. Is there a large scale system available for commercial operations? Is scale-up from the bench to full scale readily achievable or will different technologies be required at different scales? Is there a bench scale system available to perform early stage parametric studies? These are common questions facing process development engineers considering centrifugation for liquid/solid separation.

Scalability was a primary goal in the development of the CARR process centrifuges. CARR, founded in

1992, developed two product lines: Powerfuge® and ViaFuge®. Both product lines have geometrically similar models at scales from bench top through commercial, making scale-up relatively straightforward. This intra-platform scalability, along with other enabling features and strengths of the technology, resulted in rapid acceptance for targeted applications within the biotechnology, pharmaceutical, and specialty chemical industries.

Both CARR product lines were acquired in 2003 by Pneumatic Scale (a division of Barry-Wehmler Inc.). IMPACT recently visited Pneumatic Scale's manufacturing facility in Clearwater, FL and met with their technical and marketing staff. Mike McLaughlin, Director of Operations of the Clearwater Facility, was clearly excited about the recent growth and

strong revitalized interest in the CARR technology, particularly within the biopharmaceutical industry.

IMPACT has acquired a CARR Pilot system at its Devens, MA laboratory in order to perform application testing within the Northeast Region. We welcome visitors who would like to see the CARR technology or perform an application test.



CARR Powerfuge P6

### POWERFUGE®

**Description:** A variable-speed, high G-force (up to 20,000 x G) solid bowl centrifuge with automatic solids removal. Ideal for high density feeds without dilution.

#### Applications:

- Biopharmaceuticals
  - E. coli (whole cell/cell debris/IB harvest)
  - Yeast (pichia, etc.)
  - Proteins & Vaccines
- Specialty Chemicals
  - Pigmented inks
  - Metals/Catalysts
  - Thixotropic/Amorphous materials

### VIAFUGE®

**Description:** A variable-speed, low shear centrifuge with fully contained recovery of shear-sensitive cells or particles, and supernatant.

#### Applications:

- Biopharmaceuticals
  - Mammalian cell harvesting
  - Insect cell harvesting
  - Density gradient separations of cells or particles
- Specialty Chemicals
  - Colloidal metals

## Mapping Work Flow in Process Development Using IDEF0

In most chemical manufacturing processes, the process flow is diagrammed, monitored, and controlled. This structured, disciplined approach helps maximize the quality, throughput, and process efficiency, and it serves as one of the tools for performing process improvement.

A similar approach is frequently applied to defining how information flows through technology development organizations. Large amounts of

information (customer requirements, functional specifications, experimental data, operating procedures, design standards, etc) flow through various departments including marketing, research, process development, quality control, manufacturing, and quality assurance. Clearly defining, articulating, and enforcing a process for this information flow enhances efficiency, morale, and productivity in a technology development organization.

#### Typical failures include:

- Research fails to document all necessary experimental parameters, causing delays in process development during process scale-up.
- Critical specifications for a customer feasibility study are omitted by marketing, causing inapplicable or incorrect results.

- Critical pre-screening tests are circumvented to expedite schedules causing eventual rework and lost time.
- Preventive maintenance or spare parts lists are not developed or transferred from Process Development to Production, resulting in high process downtime.

IMPACT has successfully applied IDEFO (Integrated DEFINition model 0 – NIST 1993) (see Figure 1) to technology development organizations. In some cases, we have even developed customizable software platforms that combine process workflow diagrams with direct links to project documents and document templates for each step of the process. There are also commercially available software packages that

target the same capabilities. Whether developed internally or purchased from a software vendor, implementing a formal, structured process work flow provides the following benefits:

- Information flow is easily viewed, tracked, captured, and controlled by the entire organization or project team.
- Quality of work production is enhanced through consistency in procedures and documentation.
- The entire organization works faster and more efficiently.
- Institutional knowledge is consistently captured.

Establishing and improving work processes is a fundamental management role aimed at improving quality, throughput, and efficiency. IDEFO has proven to be a very valuable element of work process improvement, and one that fits in well with the six sigma approach of DMAIC (Define, Measure, Analyze, Improve, and Control).

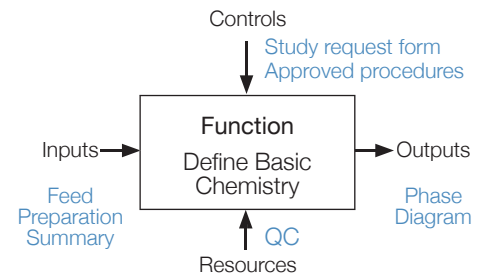


Figure 1: Standard IDEFO approach is adapted to map work process flow.

## Thermal Gradients: Another Variable in Optimizing Centrifugation Performance

Separation performance and scale-up of process centrifuges are often modeled by either the Sigma or G-area models. Sigma, developed by Ambler in 1952<sup>[1]</sup>, is an index of centrifuge separation performance, which is conceptually the area of a gravity settling tank that gives equivalent performance to that of a given centrifuge. Application of Sigma to a batch centrifuge is straightforward, as there is no flow involved.

To apply Sigma to process centrifuges (wherein the feed flows through the bowl during the separation), Ambler assumed that plug flow adequately described the flow pattern in the bowl. It is now understood that flow patterns in process centrifuges deviate significantly from plug flow. Actual flow patterns depend on the type of centrifuge and the operating conditions.

For the case of solid bowl centrifuges - which include imperforate basket, decanter, chamber bowl, and tubular bowl centrifuges - the G-area model has been proposed as a more appropriate model than Sigma. Leung presents the G-area model in detail in his 1998 book, "Industrial Centrifugation Technology"<sup>[2]</sup>. According to the G-area model, flow traverses the liquid

pool contained in the bowl as a thin boundary layer on the inner surface of the pool. The remainder of the liquid in the pool rotates in solid body rotation without appreciable internal flow.

Recent experimental studies of Powerfuge imperforate basket centrifuges<sup>[3,4,5]</sup> and decanter centrifuges<sup>[6]</sup> concluded that flow patterns in these machines are not well described by either plug flow or boundary layer flow. Bowl flow patterns were affected by several factors including: g-force, feed flow rate, accelerator efficiency, and temperature gradients. The resulting changes in flow patterns were shown to have a marked effect on separation performance.

The finding that the temperature gradient between the bowl wall and the feed liquid has significant effects on flow and separation was unexpected and not previously reported. The practical application of this effect to fine tune separation performance is the subject of a patent assigned to Pneumatic Scale Corp.<sup>[7]</sup> The most significant changes in flow patterns are dependent upon whether the bowl wall is warmer or colder than the feed liquid. Examples of these effects are shown in the residence time distribu-

tion study of Figure 3. In this study, a tracer was injected into the feed liquid at dimensionless feed volume  $V/V_b = 0$ . In Figure 3,  $C/C_0$  is the centrate tracer concentration divided by the feed concentration. These results show that the temperature profile within the centrifuge can be used to affect and control the flow pattern within an imperforate basket centrifuge. The results for the heated jacket fall very close to the CSTR curve, representing a well-mixed vessel. The cooled jacket results tend somewhat towards boundary layer flow.

Which flow pattern is desirable and how can this phenomenon be used to an advantage? Studies<sup>[3,4,5]</sup> have been performed to better understand the effects of different flow regimes on both total separation efficiency and particle classification. Better separation efficiency has been observed during well-mixed conditions induced by thermal buoyancy currents. Concurrently, boundary layer flow has been shown to better match theoretical predictions and achieve "sharper cuts" when classifying particles, particularly when operating at lower g-forces. The latter finding is illustrated by Figures 7.17 and 7.18 in Solid-Liquid Separation, 4<sup>th</sup> Edition<sup>[5]</sup>.

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Hands-On Process  
Development & Scale-Up

(continued from page 3)

In conclusion, the thermal profile within solid bowl centrifuges is an important variable that should be considered in addition to bowl speed, flow rate, and bowl geometry when optimizing centrifugation performance.

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FIGURE 2

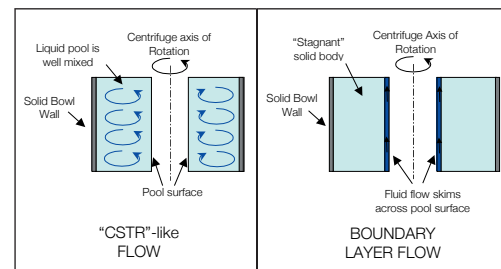
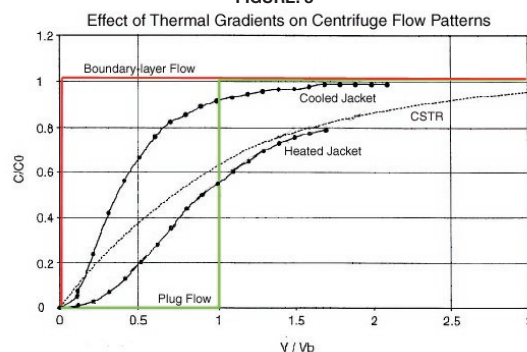


FIGURE 3



## Reader Feedback Request: Outsourcing Process Development?

Outsourcing drug development (preclinical studies, clinical trials, formulation) and manufacturing are common practice today in the biotechnology/pharmaceutical industries with favorable economics, particularly for small to medium size companies. So why is it less conventional to outsource process development and scale-up?

Outsourcing process development and scale-up should, in theory, have many of the same benefits to clients as those for outsourcing drug development and manufacturing: immediate access to a team of highly skilled engineers, established infrastructure, less

permanent staffing, efficient work processes in place, and less overhead.

IMPACT is in the process of examining this question in an article to be published later this year. Understandably, we have strong opinions on this subject, but we would like to poll the readership and get some feedback as to why you think this potential service has not substantially evolved within the biotechnology/pharmaceutical industry. We'd like to hear your thoughts and insights on this subject. Please send comments to [info@impact-tc.com](mailto:info@impact-tc.com). Thanks!



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## About Our Organization

IMPACT Technology Consultants is a team of experienced, advanced-degree chemical engineers with extensive backgrounds in chemical process technology development, scale-up, commissioning, and optimization.

Our mission is to provide process development, scale-up and engineering assistance to all industries including specialty chemical, pharmaceutical, biotech, metallurgical, and medical equipment/devices.

IMPACT also operates a scale-up and process development laboratory located at 88 Jackson Road, Devens, MA. The facility responds to frequent requests from clients to provide an off-site capability in performing process or product research, scale-up, optimization, and troubleshooting experiments.