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Key Terms and Trends in Manufacturing and Supply Arrangements

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Recent Manufacturing and Supply Chain Issues in the News

MEDTECH

Medtronic issues new warning after finding another defect in discontinued HeartWare pump

By **Andrea Park** · May 2, 2022 07:27am

The system was approved by the FDA in 2012 for implantation in patients with severe heart failure to help pump blood from the left, right or both ventricles to the rest of the body.

When sales of the implanted heart pump were stopped last June, Medtronic advised the approximately 4,000 patients already using the device not to have it removed, citing the risks associated with the surgical procedure. Instead, they were to continue using the HVAD system normally, with Medtronic pledging to provide continued technological support.

The new issue stems from a welding defect that may be present in the internal mechanism of some of the pumps, Medtronic said. The defect allows moisture into the device's center post, corroding the magnets that keep the impeller rotating around the post.

Of the three patients whose pumps were removed and submitted to Medtronic for investigation, two died after their devices were replaced.

Novartis halts US production of cancer radiotherapies, citing potential quality issues

By **Angus Liu** · May 5, 2022 09:44am

Novartis is hitting the brakes on manufacturing its two marketed radioligand therapies for cancer treatment mere weeks after trumpeting an FDA approval.

Novartis has temporarily stopped producing its neuroendocrine tumor therapy Lutathera as well as its freshly FDA-approved prostate cancer drug Pluvicto at facilities in Ivrea, Italy, and Millburn, New Jersey, the Swiss pharma said Thursday.

The company is taking the dramatic action "out of an abundance of caution as a result of potential quality issues identified in its manufacturing processes," it said. A Novartis spokesperson declined to offer additional details on the nature of the problem.

Thanks to the abrupt manufacturing mishap, Novartis has stopped delivering Lutathera to customers in the U.S. and Canada, and Pluvicto in the U.S. The surprising supply

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The suspension will affect commercial and clinical trial supplies. The company will not be delivering Lutathera to the U.S. or Canada and will not be delivering Pluvicto to the U.S. Novartis anticipates that some doses of Lutathera will be available in Europe and Asia from its production site in Spain, although delivery delays are expected.

Thermo Fisher, Charles River join robotics outfit Multiply Labs' quest to automate cell therapy production

By **Fraiser Kansteiner** · May 5, 2022 06:30am

On a quest to automate manual portions of the cell therapy production process, Multiply Labs is arming itself with two more pieces of industry-leading tech. The new kit comes on board a little less than a year after the robotics outfit unveiled a consortium aimed at building a robotic manufacturing system to make cell therapies on an industrial scale.

After recruiting an initial team that included Cytiva and the University of California, San Francisco (UCSF), Multiply Labs is adding major players in Thermo Fisher Scientific and Charles River Laboratories, the companies said Thursday.

With Multiply in charge of robotics and UCSF covering the cell manufacturing process itself, Cytiva, Thermo Fisher and Charles River will help pave the way for automation of bioreactors, incubators and quality control testing, respectively.

The New York Times

Emergent Hid Evidence of Covid Vaccine Problems at Plant, Report Says

The report sheds new light on executives' worries about deficiencies in the company's quality control systems at its troubled Baltimore plant; no contaminated doses were ever released to the public.

Emergent destroyed up to 400M COVID-19 vaccines, far more than previously known: report

By Zoey Becker • May 10, 2022 11:04am

Emergent's failures cost public funds as well as "desperately needed vaccines," according to the congressional report. The company disputes many of the report's findings.

After conducting its probe, the committee found Emergent was warned multiple times that manufacturing programs at the facility could lead to contamination. Deficiencies included persistent problems with mold, poor disinfection of plant equipment and inadequate employee training.

Officials with both Johnson & Johnson and the Trump administration's Operation Warp Speed inspected Emergent's Baltimore site in June 2020. Both audits revealed subpar plant conditions and questionable employee practices. The issues were not remediated, leading to three sperate occurrences of mass vaccine contamination in October 2020, December 2020 and February 2021, according to the congressional report.

"We are not in full compliance yet—BUT—we are making [vaccine] batches NOW," Emergent's senior director of quality control wrote in an internal email, as disclosed in the report. "Our risk is high!"

Agreements Related to Manufacturing and Supply Agreements

Related Agreements

- Quality Agreement
  - Inapplicable if the deliverable (e.g., drug substance, drug product, device) being manufactured and supplied is not subject to GMP.

- Safety Data Exchange Agreement
  - Also called Pharmacovigilance Agreement.
  - The holder/owner of marketing authorization of **drug products** must maintain a global safety data base to aggregate and submit safety reports to applicable regulatory authorities in a timely manner.

Key Manufacturing and Supply Arrangements

Key Manufacturing and Supply Arrangements

- Manufacturing and Supply of:
  - Types of Products
    - Drugs (e.g., drug substance, drug product, finished products)
    - Device (e.g., components, finished products)
    - (Digital Health)
  - Stage of Products
    - Clinical vs. Commercial
    - Non-GMP Compliant vs. GMP Compliant

Provisions That Require Commercial and Operations Input

Payment Related Terms

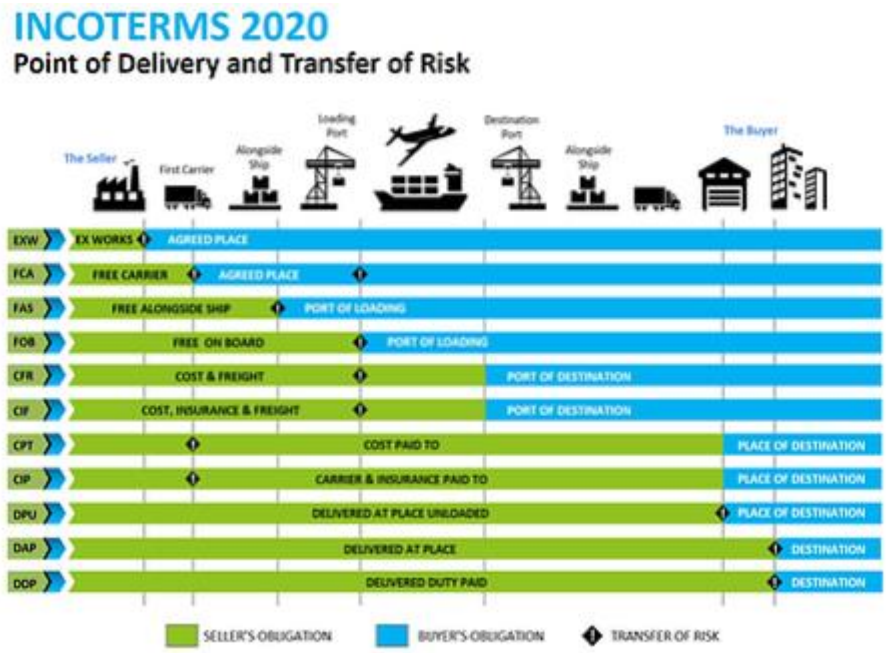
- Pricing
  - Cost of goods sold
  - Fixed price
  - % of sales
  - Tiered pricing
- Price Increase
  - Frequency
  - Amount of price increase with or without buyer's consent
- Currency, Currency Conversion and Blocked Currency
- Tax

Order Related Terms

- Purchase Order
  - When a purchase order can and should be submitted
  - When a purchase order is deemed accepted
  - Acceptable variations from binding forecasts, if any
- Rolling Forecasts, Binding Forecasts, Non-Binding Forecasts
- Lead Time, Shelf Life, Delivery Date
- Minimum Purchase Requirement

Order Related Terms (Continued)

- INCOTERMS
  - Set of 11 individual rules issued by the International Chamber of Commerce (ICC), defining the responsibilities of sellers and buyers for the sale of goods.
  - Each Incoterms rule clarifies the tasks, costs, and risks to be borne by buyers and sellers.



https://grow.exim.gov/blog/incoterms2020#_ftn1

Use of Subcontractors by the Service Provider

- Should the service provider have the right to engage subcontractors:
  - Freely vs. with the [prior] notice to customer vs. with prior consent of customer?
- Considerations:
  - Does customer want to vet subcontractor prior to having them engaged?
  - Is it okay for subcontractors to have access to sensitive or proprietary information [without customer's consent]?

Use of Subcontractors (continued)

- Best Practices Regarding Subcontractor Agreements
  - Require the agreement to in writing;
  - Require the agreement to be consistent with the terms of the customer-service provider agreement;
  - Require that the customer have the right to review such subcontractor agreements; and
  - In the event of breach of the terms by the subcontractor, the service provider would be liable for such breach.

Provisions That Require Alignment with the Quality Agreement

Product Warranty

- Product Warranty
  - GMP products must comply with:
    1. Applicable **specification**
    2. **GMP** (and any and all applicable law)
    3. Applicable terms of the manufacturing and supply agreement and the **quality agreement**

Product Warranty (continued)

- Non-Conforming or Defective Products are those that fail to comply with the Product Warranty
- Latent Defects are defects found not immediately after delivery
- Remedies for Non-Conforming or Defective Products
  - Return or refund, which should not be the sole remedy available to customer

Recalls, Audits, Inspection

- Quality Agreements must set forth each party's **legal obligations** related to the maintenance of the quality of the products – e.g.,
  - Who should sign for the release of the products?
  - If there is a recall of the product, which party would be responsible for notifying whom;
  - How many times per year does customer have the right to inspect the facilities of service provider?

- However, quality agreements do not address the contractual liabilities or remedies if there is a breach of the terms of the manufacturing and supply agreement or violation of applicable law.

Recalls, Audits, Inspection

- Customer should have the right to participate in any inspections or audits conducted by regulatory authorities that [directly] relate to customer's product.

- The scope of books and records that customer can access during audits and inspections should include those related to quality, as well as other records to confirm the performance of the entire agreement (e.g., order, payment and other commercial related terms).

Complex Legal Provisions

Force Majeure

- Service Providers are trying to broaden out the definition of “force majeure events.”
- Although negotiable, read carefully so that only true “natural and unavoidable catastrophes” are included in the definition.
- A party experiencing a force majeure event should be excused from performing activities under the agreement without being in breach thereof only if such event [directly] affects such performance and only so long as such event exists.

Force Majeure (continued)

- A party experiencing a force majeure event should have the obligation to promptly notify the other party.
- A party experiencing a force majeure event should use [best / reasonable] efforts to remove such events so that it can resume performing under the agreement.
- If such event continues, customer, not the service provider, should have the right to terminate the agreement.

Indemnification

- Limit to third party indemnification only.
- As the applicant/owner of regulatory filings, marketing authorization holder and/or the manufacture of devices, customers will be exposed to end user and regulatory authority claims, even if the cause of such claim, in whole or in part, was the service provider.
- Ensure that service providers agree to indemnify third party “product liability” claims, to the extent cause by such service provider.

Limitation of Liability

- As with other commercial agreements, service providers want to limit their liability exposure.
- Each party's liabilities are often limited to direct damages, but it is also quite customary to exclude from such limitation to those claims arising or related to confidentiality, [gross] negligence, willful misconduct or fraud, and third party indemnification.
- Service providers may also try to cap their liabilities under the agreement to a certain amount, but the above exclusions should apply.

Supply Chain Shortage

- Service Providers will rarely agree to expressly assume risk for supply chain shortages.
  - More often than not, service providers would agree to treat customer similarly with other customers and pro-rate the distribution of products based on a formula.

- The risks of supply chain shortage caused by the service provider would be addressed to the extent possible by
  - Accessing two or more supply chains;
  - Creating safety stocks; and
  - Indemnification and breach of contract claims.

Termination

- Even if a customer may terminate the agreement at-will, customer will need to pay for all accrued fees as of the effective date of termination, including non-cancelable costs.

- Service providers may also demand termination fees (e.g., for canceling reserved manufacturing slots).
  - Termination fees are highly tailored to reflect lead times and the nature of the product.

- Service providers should not have a right to terminate the agreement at-will.