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Manufacturing Strategies for BRIC(K)* Countries

**Brazil, Russia, India, China (and Korea)*

Philipp N. Hess[1] and Luiz F. Cerqueira[1]

[1]PHA – Philipp Hess Associates
NL-2317NB Leiden, The Netherlands

[2]LFC Consultancy, LLC.
Orem, Utah 84058, USA

Correspondence: Philipp N. Hess, Lavendeltuin 11, NL-2317NB Leiden, (philipphess@ziggo.nl)

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Abstract
Developing a manufacturing strategy for BRIC(K) countries requires careful consideration of "Everything" (that can impact the size of the local plant and required capacity output over time).
For example, modular expansion is tremendously important for profitability while automation is a major protection of company's profit. Challenges are cost pressures, limited biotech exposure of local regulators, developing infra-structure, and inexperienced plant operations work-force.
A SmartFactory is an enabeler of modern and cost effective manufacturing strategies efficiently mitigating those challenges. The design and cost modeling exercise leading to a SmartFactory will be described.

As summarized in a paper on best practices for successful implementation of single-use technology (1), single-use bioprocessing facilities play their role as clinical trials and low to mid volume market supply facilities. In the future, single-use bioprocessing facilities will play an increasing role as new product technology will need smaller bio-processing capacities (2).

In countries like **Brazil, Russia, India, China (and Korea)** low initial investment, portability, and flexible add on capacity are even more the key to a successful Manufacturing Strategy.

The need for **Local Manufacturing** is different in each of the countries an may be caused by

- no, limited, or unknown acceptance of foreign clinical data
- barriers against drug imports
- materials may still need to be imported
- incentives for local manufacturing
- no experienced local biotech contract manufacturer's

Elements of **Entrepreneurial Vision**

a) acquiring knowledge by learning from the experience from abroad.
b) alternative technologies and process controls
c) successful conceptual design principles
d) edgy engineering (simplification & flexibility)
e) demonstrated efficient practical operational concepts

In the past, the **Conceptual Design** was a specific function of the Technical Area. Nowadays it is an "Executive Function"; A critical part of the Business Plan.
The modern Business Plan requires Plans B, C, D, …., to timely adapt to the external changes, which impact the initial plan. These alternatives must be built-into the SmartFactory concept. "Sizing" the 5 year sales projections and product introductions allows Flexible and Strategic Design (avoiding idle capacity).

The logical balance between the enthusiasm of Sales, the skepticism of Finance, the drive of R&D and the conservative approach of Operations (to ensure product is timely delivered) is an "**Executive Function**" with positive impact in the plant design, construction and expansion.

Figure 1 -Manufacturing Strategy - Critical Information

Early manufacturing requirements are product for clinical testing but the clinical/regulations may vary e.g.: Product registration with results from abroad and confirmatory tests with reduced enrollment of subjects locally, register product with Phases I, II e III carried-out locally, or register product with a combination of the above,
When, based on clinical tests shall the scale-up for validation and commercial production start? E.g. the regulators in the PRC are expecting full scale manufacturing during Phase III; That leads to initial considerations on the scale-up, sizes and timelines based on: The estimated range of sales projections/therapeutic dosage/process yield, as well as initial considerations on the staggered investment (for maximum investment "safety" as a function of the performance of the product in the clinical trials and sales projections).

Key Principles

Comprehensive Overall Master Plan: begin with the destination in mind (a "safe flight plan")
Strategies to Adapt ("in-route"): knowing where to go, create alternatives to get there (Plans B, C, D….)
Full Alignment: with functional areas and the business plan
Modular Expandability: use money after money is flowing-in.
Pre-set expandability routes will ensure operational continuity when expanding the facility (critical in growth mode).
Simple Facility Design: complication costs money. Biotech does not need to be complicated anymore.
Ultimate process control capability: clever and economical automation.
"Extreme" Personnel Training: involve key people as early as possible in the project, invest on them, give them some equity (to avoid losing them). They are the ones who will protect your money on the shop-floor.

During a number of (award winning) manufacturing facilities projects, the authors integrated concepts, that pave the way towards the factory of the future for commercial biologics manufacturing. Those facilities are flexible, multi-product, designed to minimize manufacturing

costs and product cycle times. In all cases, a radical debottlenecking/cost modeling exercise ensured that a highly flexible configuration would deliver speed and cost benefits.

For the SmartFactory, the **cost modeling exercise** is presented in figure 2.

Requirement Model - Assumptions
MAb Dose: e.g. 2 g/L per patient per year
Clinical requirement and timeline
Market Size e.g. 20'000 patients
Sales Curve
Requirements combined
E.g. 4–5 products
E.g. 1– 4 campaigns per year

Process Model - Assumptions
Process Assumptions
Batch Size USP: 1000 L - 2000 L
Batch Size DSP: 1-2 x 3 kg/batch
Titer 1.5 – 3.5 g/L
Yield Harvest to Bulk: 66.66%
Cycle times analysis

Aim for SU equipment
Chromatography flow <510 L/h
Ultra-/Diafiltration <10 m3
Balance USP and DSP

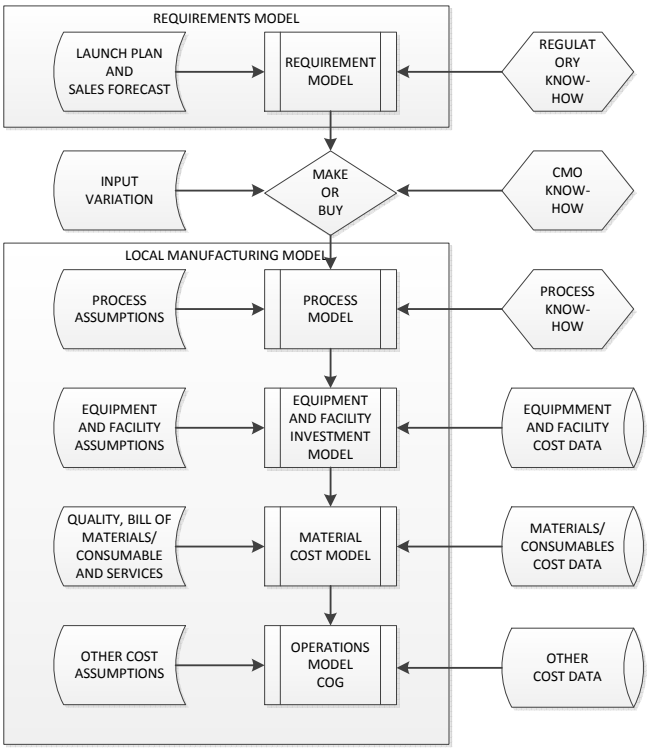

Figure 2 – Cost modeling exercise

For the **SmartFactory**, the conceptual design objectives were

to minimize facility investment by aiming
to minimize unnecessary space usage
to reduce the amount of segregation by adhering to closed systems throughout the process
to design media and buffer preparation according to lean principles where storage is minimized
to minimize processing in this facility where the product is brought in its final formulation where there regulator expects higher classified clean-room area (e.g. class C for formulation buffer preparation)
to minimize the need for process utilities such as highly purified water clean steam etc. and to have a logical, modular expandability route on the level of building, built-out, equipment and automation

Conceptual design and adaptation to a running project as well as the **cost model outcome** will be discussed.

For the **project execution** – speed and precision are key objectives.
Our preferred execution approach is the following hands-on management on all levels (Executive, International and Local).
For e.g. the PRC we would do an entire International Conceptual Design while the Preliminary and Detailed Design would be performed by a local Engineer checked by international design team. During the Construction Phase, process equipment and consumables would be procured internationally, while construction and installations procured locally. Construction should be managed by local PM supported by CM resources and quantity surveyors

For the **operation** – discipline, quality and consistency are the key objectives.
For mitigating single-use supply risks our recommendation would be to have

Two suppliers for standard bags and tube-sets
A process-vessel backup strategy e.g. splitting tank farm among two suppliers
Automation which is supplier independent and pre-configured for at least two suppliers

Summary

Developing a manufacturing strategy for BRIC(K)* Countries requires careful consideration of "Everything" (that can impact the size of the local plant and required capacity output over time). For example, modular expansion is tremendously important for profitability while automation is a major protection of company's profit.
Challenges are cost pressures, limited biotech exposure of local regulators, developing infra-structure, and inexperienced plant operations work-force.
A SmartFactory is an enabeler of modern and cost effective manufacturing strategies, efficiently mitigating those challenges

References

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