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Progress by innovation

SUSTAINABLE DEVELOPMENT GOALS

Lean Local API Manufacturing

INTRODUCING UNIDO'S APPROACH

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This publication was prepared by the Health Industry technical team within the Division of SME Competitiveness, Quality and Job Creation (SME) of the UNIDO Directorate of Technical Cooperation and Sustainable Industrial Development (TCS).

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CONTENT

INTRODUCTION

The world is experiencing devastating consequences due to pandemic COVID crisis that halted many manufacturing operations in the pharmaceutical industry globally. The pandemic situation reminded us of the importance of resilient, competitive, and globally more equally distributed manufacturing of pharmaceuticals, vaccines, PPI, diagnostics, and by far the most inadequately produced active pharmaceutical ingredients (API), particularly at low and middle-income countries.

UNIDO is highly dedicated to drive progress of lean local production of all pharmaceutical and biopharmaceutical raw materials, APIs and finished products by fostering innovative tools for technology transfer including all interested potential stakeholders. Encouraging local production of APIs based on international GMP standards in developing countries can provide better access to medicines. APIs have become an increasingly important part of the pharmaceutical supply chain, where they represent the most valuable and clinically effective components, and offer real security of supply.

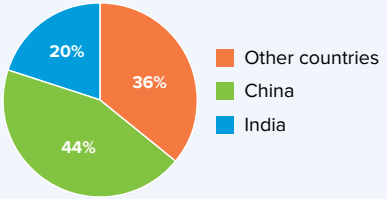
Facts

India and China currently dominate in the production of APIs, intermediates, and other pharmaceutical ingredients, and account for up to 70% (2023) of global production.

According to market forecasts, the active pharmaceutical ingredients market is expected to increase from USD 193.15 billion in 2023 to USD 285.29 billion.

by 2028 Globally, 60.5% of API is produced in Asia Far East, 27.9% in Western Europe, 4.6% in North America, and 7% in the rest of the world (European Fine Chemicals Group, 2022). There is currently limited API production in Africa, except for South Africa where the APIs for paracetamol, codeine, and several cancer drugs are produced, and Pharmakina in the Democratic Republic of Congo (DRC), which produces Quinine API, and several new projects in Nigeria and Egypt. Currently, China and India are the leading suppliers of pharmaceutical raw materials and excipients worldwide (MAA Khan, J. PHARM POLICY PRACT 2024). Thus, in order to empower local companies and create independence from import and build a self-sustainable ecosystem, local production of APIs in developing countries, based on lean, six sigma principles with elements of circular economy and waste management is a priority and commitment for international health associations and all engaged stakeholders including private sector, pubic institutions governments, regulatory authorities and academia.

Figure 1: Global API production (% of volume)



Source: Economies 2021*

* India's Road to Independence in Manufacturing Active Pharmaceutical Ingredients: Focus on Essential Medicines, Economies 2021.

Challenges

- Lack of national API capacities and capabilities
- Lack of relevant skills
- High cost of local manufacturing
- Lack of interlinkages between different sectors and associated industries
- Limited access to regional and global markets (small local market size)
- Low compliance with international GMP standards

SOLUTION

UNIDO's model on Lean Manufacturing coupled with Six Sigma, Circular Economy, Waste Management and Digital Transformation

▶ What is an API?

Figure 2: Definition of API

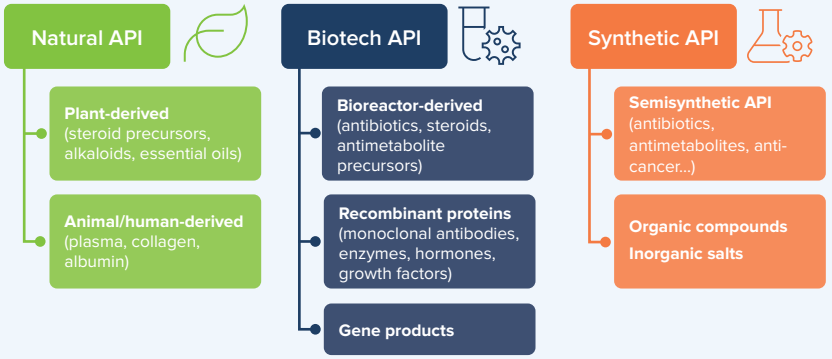
"Any substance or mixture of substances, intended to be used in the manufacture of a medicinal product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body".

Source: EU-GMP Legislation

Active Pharmaceutical Ingredients of good quality are core to the manufacturing of effective and safe essential drugs. The price of APIs is the main cost driver for manufacturing. Only a limited number of large manufacturers of finished pharmaceutical products have their own API manufacturing capabilities, and none of them can make all required APIs in-house. API manufacturing is a very complex and technically challenging process that involves the synthesis of chemicals (synthetic or semi-synthetic APIs), production of biochemical compounds (Biotech APIs) or extraction APIs form natural sources like plants, animals and humans (plant-based APIs).

▶ Types of APIs

Figure 3: Different sources of API



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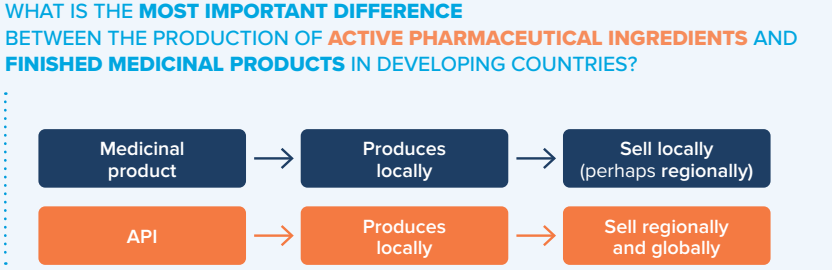
The production of APIs is distinct from finished medicinal products. A key difference, especially in developing countries, is that finished medical products are predominantly manufactured for local markets, or targeted at regional markets, while APIs are usually produced for global or at least regional export. Therefore, API production must adhere and comply with international GMP standards.

Figure 4: Comparison of production



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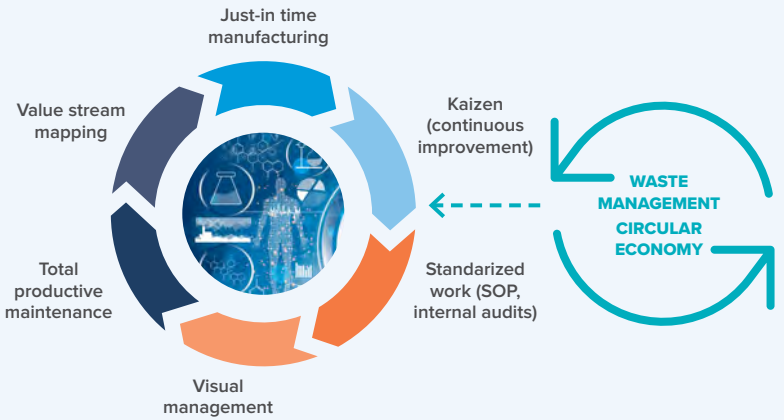
Lean Six Sigma API Production: short overview

Lean Manufacturing

Lean manufacturing: improving productivity considered a waste management by mapping processes and identifying improvement areas, including circular economy and digital transformation.

Figure 5: Lean manufacturing



Six Sigma

Sis Sigma: identifying root cause, improving quality and reducing the level of defects by analysis, validation, solution development and standardization of final actions.

Figure 6: Six Sigma methodology

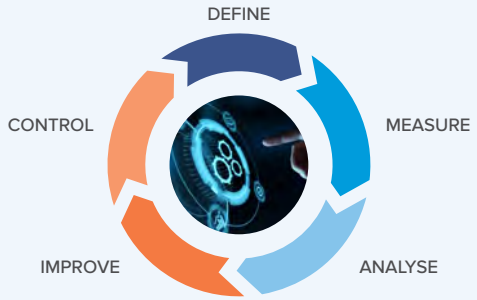


Figure 7: Synergy between Lean production and Six Sigma methodology

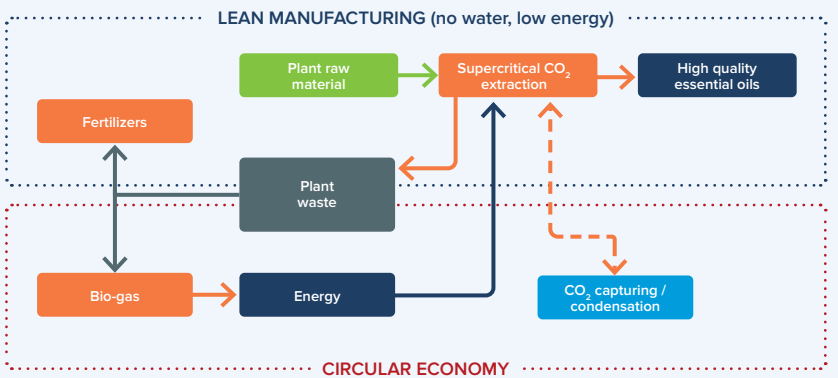
Six Sigma methodology uses a structured DMAIC (Define-Measure-Analyze-Improve-Control) approach to tackle problems with unknown root causes and/or unknown solutions. When it is coupled with Lean methodology, it can improve profits and increase customer satisfaction, and represents an integrated, superior approach. The combination of six Sigma/Lean uses the following main principles:

Examples

A Lean API production from plant raw material

Figure 8: Lean production of plant-based API (essential oils) by re-using CO_2 as extraction vehicle and utilizing used raw material as biofuel

Plant-derived API. Production of essential oils by lean API extraction



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Our innovative approach to plant-based API production—especially for essential oils—integrates Lean production principles with environmental responsibility by reusing CO_2 as an extraction vehicle and converting used raw material into biofuel.

Key benefits:

1. **LOWER ENVIRONMENTAL IMPACT**

   CO_2 Reuse: Recycling CO_2 reduces emissions and minimizes the need for new solvents, significantly lowering our carbon footprint.

   Biofuel from Biomass: Residual plant material post-extraction is repurposed as biofuel, reducing waste and supporting renewable energy use on-site.

2. **COST SAVINGS AND EFFICIENCY**

   Reduced Material Costs: Recycled CO_2 and biofuel lower operational costs by minimizing raw material and energy expenses.

   Energy Efficiency: Self-generated biofuel powers parts of the production facility, fostering a self-sustaining system.

3. **ENHANCED QUALITY AND YIELD**

   Precise CO_2 Extraction: Supercritical CO_2 extraction at controlled temperatures preserves essential oil integrity, leading to higher quality and more consistent yields.

4. **SUSTAINABLE MARKET ADVANTAGE**

   Green Certifications: Eco-friendly practices appeal to markets focused on sustainability, enhancing competitiveness and aligning with global environmental goals.

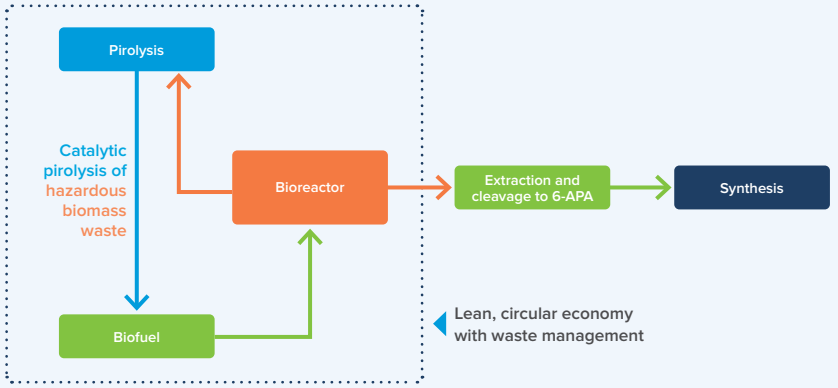
This Lean, eco-conscious production model offers an efficient, sustainable, and cost-effective approach to plant-based API manufacturing, aligning high-quality production with environmental responsibility.

Examples

B Lean API production of semi-synthetic antibiotic

Figure 9: Lean manufacturing of semi-synthetic API (amoxicillin) including optimal waste management and renewable energy

Semi-synthetic API. Production of amoxicilin by lean API bioreaction



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Lean Manufacturing of Semi-Synthetic APIs (Amoxicillin) with Optimal Waste Management and Renewable Energy

Our advanced approach to producing semi-synthetic APIs like amoxicillin combines Lean manufacturing principles with sustainable practices, focusing on optimal waste management and the integration of renewable energy sources.

Key benefits:

1. **REDUCED ENVIRONMENTAL IMPACT**

   Waste Minimization: By optimizing production steps and recycling solvents and other materials, we significantly reduce hazardous waste output.

   Efficient Waste Treatment: Waste is carefully treated to minimize environmental impact, ensuring compliance with strict regulations.

2. **COST SAVINGS AND PROCESS EFFICIENCY**

   Reduced Material Waste: Lean practices streamline the use of raw materials, minimizing waste, lowering costs, and increasing efficiency across production cycles.

   Energy Efficiency: The integration of renewable energy, such as solar or biofuel, powers key parts of the facility, reducing dependency on fossil fuels and decreasing overall energy costs.

3. **ENHANCED QUALITY AND CONSISTENCY**

   Precision in Production: Lean manufacturing improves the accuracy of each step, enhancing the consistency and quality of amoxicillin batches, a crucial factor in pharmaceutical production.

4. **SUSTAINABLE MARKET ADVANTAGE**

   Eco-Conscious Labeling: Sustainable practices position us as leaders in green manufacturing, appealing to environmentally focused markets and aligning with global sustainability goals.

   Regulatory Compliance: Lean waste management ensures we meet or exceed environmental regulations, enhancing our reputation and market appeal.

Our Lean production approach for semi-synthetic APIs like amoxicillin combines efficiency, sustainability, and cost savings, setting a high standard for responsible pharmaceutical manufacturing.

KEY TAKEAWAY POINTS

Active pharmaceutical ingredients of good quality are core building blocks of effective and safe drug manufacturing, constituting the most important ingredient for achieving desired health effect.

Local lean, environmentally sustainable API manufacturing in low and middle-income countries has the potential to yield significant economic and social benefits, lead to lower cost of medicines with reduced reliance on imports and foreign exchange savings, and reduced supply chain fluctuations.

Local production of APIs in developing countries, based on lean, six sigma principles with elements of circular economy and waste management is a priority and commitment for international health associations including stakeholders from private sector, public institutions, governments, regulatory authorities and academia.

Global collaboration is required to improve the capabilities of local lean API manufacturing in low and middle-income countries by mobilizing new health-focused, non-profit funds and grants.

ACRONYMS

API	Active Pharmaceutical Ingredient
CO_2	Carbon Dioxide
DMAIC	Define-Measure-Analyze-Improve-Control
DRC	Democratic Republic of Congo
EU	European Union
GIZ	*Gesellschaft für Internationale Zusammenarbeit GmbH*
GMP	Good Manufacturing Practice
PPI	Proton Pump Inhibitor
SME	Small and Medium Enterprise
UNIDO	United Nations Industrial Development Organization
USD	United States Dollar

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