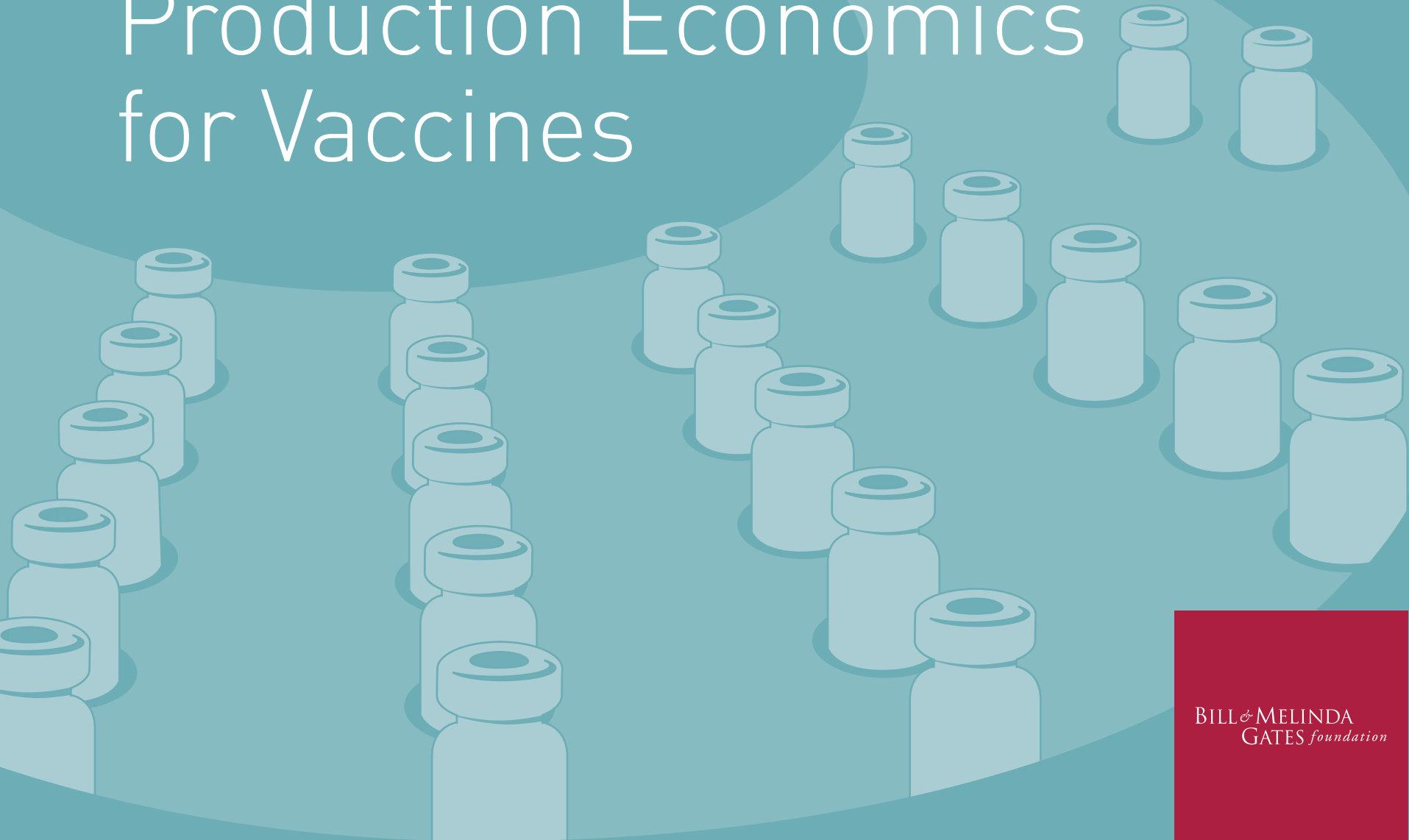


Production Economics for Vaccines



CONTACT INFORMATION

It is the hope of the foundation that vaccine Production Economics (PE) assessments will be completed collaboratively with manufacturers through transparent dialog and data sharing. We find that this approach leads to the most accurate assessments and ultimately supports the best strategies for partnering to achieve healthy vaccine markets.

Do not hesitate to reach out to the foundation with any questions or comments on PE assessments. Please contact Robyn Iqbal or Tina Lorenson in Vaccine Delivery – Market Dynamics.

Robyn Iqbal

Senior Program Officer, Vaccine Delivery - Market Dynamics
Global Development Program

Robyn.Iqbal@gatesfoundation.org

Tina Lorenson

Program Officer, Vaccine Delivery – Market Dynamics
Global Development Program

Tina.Lorenson@gatesfoundation.org







Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation aspires to help all people lead healthy, productive lives. We are dedicated to discovering and disseminating innovative approaches to addressing extreme poverty and poor health in developing countries and improving the U.S. education system. Because our financial resources, while significant, represent a small fraction of what's needed to address these challenges, we work in partnership with governments, the private sector, and other donors and organizations to achieve the greatest possible impact.

For additional information on the Bill & Melinda Gates Foundation, please visit our website: www.gatesfoundation.org.

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Introduction

The mission of the Bill & Melinda Gates Foundation (the foundation) is to help all people lead healthy, productive lives. Specifically, the Global Development Division at the foundation works to help the world's poorest people lift themselves out of hunger and poverty, while the Global Health Division aims to harness advances in science and technology to save lives. We work with partners to provide proven tools—including vaccines, drugs, and diagnostics—and to discover novel solutions that are both affordable and reliable. Equally important is innovation in how health interventions are delivered to those who need them most.

In collaboration with Gavi Alliance partners, the foundation develops vaccine market strategies to ensure affordable and sustainable access to vaccines in lower-income countries. When investments can support our market goals, the foundation has a variety of investment tools (e.g., grants, loans, guarantees, etc.) that can create mutually beneficial opportunities with manufacturers. When evaluating and structuring these investments, we find it critical to have a strong and reliable understanding of a manufacturer's **Production Economics** (PE). Core to understanding PE, is understanding a manufacturer's fully loaded cost base for a product, from the initial costs of discovery and development through manufacturing and final packaging, with allocations made as appropriate. Throughout this handbook we use the term PE to refer to this core component. Within this handbook we also use the term **Production Economics Cost of Goods Sold (PE COGS)**¹ to refer to all costs associated with the definition of PE above.

Use of a robust and comprehensive methodology to assess PE is core to a fair and sustainable market.

Use of a robust and comprehensive methodology to assess PE is core to a fair and sustainable market—for both countries and manufacturers. Specifically, it is important for:

- Ensuring access and affordability of vaccines and other health-related products in lower-income markets; and
- Assuring that the manufacturers serving these markets earn an appropriate return on investment that allows the production of such vaccines and other health-related products to be beneficial for the manufacturer and its stakeholders.

As an organization that values vaccines and the positive impact they have on global health, the foundation recognizes the importance of balancing these two goals and in being transparent in how we evaluate PE. As such, the foundation is sharing this handbook with manufacturers and other relevant partners. This handbook contains details on the standard methodology the foundation uses to evaluate the PE of a vaccine produced by a specific manufacturer in a particular market. **We recognize that manufacturers may internally account for these costs in different ways, and the intent of developing this methodology is for the foundation to have and use a consistent and standardized approach to PE in order to evaluate different investment opportunities in a more accurate and reliable way.**

¹ While COGS is a common accounting term with a narrow definition, please note we are defining PE COGS as the costs discussed in this handbook.



Background

This handbook is focused on PE for vaccines, and specifically for vaccines intended for global health.² Vaccines save millions of lives each year and are among the most cost-effective health interventions. That said, vaccines are often too expensive for the world's poorest countries, and supply shortages as well as downstream delivery obstacles pose challenges to access.

As a collaborator on the Global Vaccine Action Plan (GVAP), the foundation is committed to a framework that aims to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. In addition, as part of the broader vaccine community, the foundation supports the innovation needed to develop new vaccines and associated delivery technologies. As such, the foundation's Global Health Division invests heavily in vaccines to prevent infectious diseases (including improvements on current vaccines as well as new vaccines), related health interventions, and supporting technologies. The foundation focuses its investments on increasing vaccine access for the 73 Gavi eligible countries with the goal of creating equal access to new and underused vaccines for children living in the world's poorest countries.

When developing strategies to achieve healthy vaccine markets and considering specific investments, the foundation is mindful of economic considerations and tradeoffs involved in the development and commercialization of a vaccine. The foundation establishes an **intervention target product profile (iTTP)** for priority vaccines to define minimal and optimal parameters for vaccines, as this helps to guide product development investment decisions. PE is one of the important parameters defined in the iTTP, as it directly informs global access and affordability.

! We recognize that vaccine pricing must be sustainable for manufacturers, and therefore the price must also incorporate profit and risk, and that acceptable values for these elements will vary by manufacturer for numerous reasons. Furthermore, having a strong understanding of PE helps the foundation and manufacturers participate in a transparent conversation about pricing to ensure that an investment will be both fair and sustainable for the manufacturer and also have the intended global health impact. When a manufacturer is willing to collaborate and contribute to the foundation's understanding of PE, our shared understanding of PE will be deeper, and subsequent conversations around investments will be more informed.

Pricing discussions aim to ensure sustainability for a manufacturer and its ability to meet the intended global health impact.

² Note that the PE methodology and principles outlined in this handbook are specific to vaccines, but may also be extended to other biologics such as monoclonal antibodies.



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How to Use This Handbook

The intention of this handbook is for use in the following ways:

1. To gain familiarity with the foundation's approach to calculating PE COGS so differences in an individual manufacturer's approach can be identified and can inform discussions (note there is not an expectation that manufacturers conform to the foundation's approach for the manufacturer's own internal accounting purposes)
2. To guide PE COGS calculations by manufacturers
3. To provide guidance for partner organizations calculating PE COGS on the foundation's or a manufacturer's behalf

The methodology outlined in this handbook can be applied to commercialized vaccines as well as to vaccines in the earliest stages of development. In many instances, an organization—be it a manufacturer or public health organization—is concerned not with the overarching PE of a vaccine, but more specifically the PE of that vaccine related to specific countries or regions, such as the Gavi market.

Further, the foundation recognizes that there are, at times, significant costs that extend beyond the PE of the manufacturer (e.g., downstream delivery) that are part of the total systems costs of a given vaccine. While the foundation is simultaneously working to estimate and reduce these costs, these costs are outside the scope of this handbook, which focuses on costs specific to a given vaccine manufacturer.

Downstream delivery costs are not included in the foundation's approach to calculating PE COGS.

Organization of This Handbook

The remainder of this handbook outlines the principles and methodologies for assessing the PE for a vaccine; it is organized into the following sections:

- **Overview** provides an executive summary of the foundation's approach to PE;
- **Data Collection Methodologies** discusses the foundation's approach to collecting data to assess PE;
- **Determining Production Economics Costs** presents an overview of the types of costs and cost categories appropriate for assessing PE;
- **Allocation of Costs** details how to properly allocate costs so the PE is specific to a vaccine and market; and
- **Impact of Economic Variables** describes micro- and macroeconomic variables as well as other economic factors that have an impact on PE over time.

NAVIGATING THE HANDBOOK

The following elements will alert you to other resources or information that may be helpful while reviewing this handbook.

Bold blue terms are jump links to and from the glossary section.



The computer icon indicates information relevant to the workbook that can be found at:

https://docs.gatesfoundation.org/Documents/PE_Vaccines_Appendix_2016.xlsm



Executive Summary

The foundation uses a standardized methodology to evaluate the PE of a particular vaccine in a particular market to ensure that all relevant cost categories are captured, and captured in a consistent way. Costs incurred throughout the product life cycle of a vaccine can be grouped into the following specific cost categories:

- **Product Development:** Costs incurred to discover, develop, and bring a vaccine to market (e.g., upfront R&D, clinical trials, regulatory approval including WHO Prequalification (WHO PQ), etc.);³
- **Facilities and Equipment:** Costs associated with fixed assets. Includes capitalized costs that depreciate over time (e.g., land, buildings, machinery, etc.) as well as ongoing costs of upkeep (e.g., repairs and maintenance, utilities, etc.);
- **Direct Labor:** Employee costs (e.g., wages, benefits) directly attributable to a specific vaccine;
- **Consumables:** Raw materials used as inputs in production of a specific vaccine;
- **Overhead:** Costs necessary for the manufacturer to incur in order to function, but not directly attributable to a specific vaccine. This handbook makes a distinction between two types of overhead: **Indirect Overhead** (e.g., plant management salaries, wages, training, etc.) for indirect expenses associated with plant management at each stage in the production process and **Corporate Overhead** (e.g., C-suite salaries, centralized back-office functions, insurance) for indirect expenses associated with the broader infrastructure of the manufacturer;

- **Commercialization:** Expenses incurred post regulatory approval associated with selling and marketing the product in the relevant market (e.g., advertising, marketing, distribution, etc.); and
- **Licensing:** Any income received (or expenses paid) for granting (or licensing) the right to use product-related intellectual property in order to produce the vaccine (e.g., technology). Any income received would be included as an offset to costs.

Along with costs incurred, these inputs impact costs—potentially reducing PE COGS—and should be included:

- **Third-Party Contributions:** All contributions (e.g., grants, loans, subsidies) from governments and other third-party (i.e., non-foundation) organizations are included to capture their impact on costs; and
- **Foundation Contributions:** All contributions (e.g., grants, loans) from the foundation are included as an impact to costs.

Third-party contributions such as grants, loans, and subsidies may reduce PE COGS.

³ The categorization between R&D, regulatory expenses, and marketing expenses can be a blurred line (e.g., clinical trials done to comply with regulatory organizations, local market registration that can be considered commercialization). As such, for the purposes of this handbook, we use the term Product Development to encompass all activities and associated costs incurred by a manufacturer to achieve commercial production of a vaccine (e.g., discovery, trials, PQ, local market registration). To the extent that a detailed breakout of these costs is available, it will be taken into account. Please note that there is also a separate Commercialization category; however it is intended only to include sales and marketing (to the extent it exists), as local market registration will fall under Product Development.



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These cost categories are designed to be general enough to cover all applicable costs. Depending on the level of detail available, each of these cost categories may represent the aggregation of a number of more detailed cost categories, or in the case of less detail, data may need to be segmented based on a reasonable allocation key in order to map to these cost categories. In either case, **it is important to confirm that costs are not double counted (i.e., by inclusion in more than one category).**

Further, the foundation’s data collection methodology as described within this handbook places an emphasis on data collection by production step, to the extent available. Collecting data and assessing the components by production step is driven by the foundation’s desire to more fully understand the drivers of PE. This understanding can shape the foundation’s investment construct to best support a manufacturer’s needs and can also help identify potential areas for cost reductions, which in turn can improve affordability and sustainability.

While the foundation recognizes that manufacturers may not keep costs in a format consistent with the production steps laid out in this handbook, to the extent possible, segmenting relevant cost categories by these four main commercial production steps allows for further insights to be made from the PE assessment.

The four commercial production steps are:

1. **Bulk:** Costs incurred in the production of the bulk product, including both upstream and downstream processes, but before any formulation, filling, and finishing occurs. For vaccine production,

bulk production is often the most complex and costly of the four steps, and typically includes a cell culture or fermentation stage followed by some combination of recovery, purification, and/or conjugation unit operations to arrive at a final bulk vaccine product;

2. **Formulation, Filling, and Finishing (Form/Fill/Finish):** Costs incurred during the production of final dosage form, including formulation (e.g., adjuvantation and lyophilization), aseptic filling, and finishing steps of the production process, including vial labeling before any secondary packaging;
3. **Secondary Packaging:** Costs incurred during packaging of the final dosage form, commonly referred to as secondary packaging. This will generally include activities such as putting finished vaccines into cartons and preparing them for shipment. This also includes all warehousing costs; and
4. **QA/QC:** Costs involved with quality control and quality assurance testing. These activities may occur at multiple points throughout the production process and therefore if possible, it is helpful to segment the related costs by the above production steps. To the extent that these costs are already embedded in the above production steps and cannot be broken out, it is important not to double count.

The diagram below displays the vaccine production process beginning with Product Development (as defined above) and moving into Commercial Production, which includes the four steps outlined previously. The fully loaded costs associated with a specific vaccine in a specific market may span both Product Development and Commercial Production.

DIAGRAM 1: VACCINE PRODUCTION PROCESS



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Data Collection Methodologies



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Inside-out vs. Outside-in
Data Collection Templates
Identifying and Capturing
Fully-Loaded Costs

Data Collection Process

The most accurate PE assessment will use the most reliable data available. Generally, this involves coordination with the manufacturer and review of available data (e.g., actuals, projections, analogs, etc.). When this information is not directly available, there are alternative means for collecting data to perform a PE assessment. Typically this involves relying on industry data (for the same or comparable vaccines), industry expert input, and/or institutional knowledge, as discussed in more detail below.

Inside-Out vs. Outside-In

While each PE assessment is unique to the facts and circumstances of the specific product and market (as well as the investment opportunity), there are generally three approaches for performing a PE assessment to understand the costs to produce a specific vaccine in a specific market:

1. **Inside-Out:** Data collection approach based on quantitative and qualitative manufacturer data and process information;
2. **Outside-In:** Data collection approach based on indirect sources of information such as conversations with third-party consultants/experts or applicable vaccine data from other sources (e.g., industry studies); and
3. **Hybrid:** A combination of the two above approaches generally comprised of using third-party sources to substantiate or augment manufacturer data and process information.

The selected approach is typically dictated by the availability and reliability of manufacturing/product-specific information. The Hybrid approach can be seen as a means to supplement an Inside-Out

approach, particularly in situations where the available manufacturer data and process information are based on early stage projections (e.g., estimates of costs at commercial scale based on pilot facility) or when product-specific projections are not available. In those cases, a Hybrid approach can account for missing or ambiguous information through the use of industry benchmarks (e.g., obtained from internal and/or external experts) or the manufacturer's experience with analog products.

When data and process information are not available, for whatever reason, using analog data can prove useful. Analog products can be later stage/commercialized products that have a similar production process as the product in question. It is also possible that different analogs can be used for each step in the production process, for example:

- The costs for a manufacturer that produces a four-valent HPV vaccine are known and a researcher wants to estimate the cost of a proposed nine-valent vaccine by the same manufacturer. The costs may be estimated by using the costs of the four-valent vaccine as a starting point and making adjustments based on known differences in the production process of the two vaccines (e.g., materials costs for additional antigens).
- A researcher wants to estimate the costs of a four-valent HPV vaccine produced by a different manufacturer. The costs may be estimated by starting with the known costs of producing the four-valent HPV vaccine and adjusting for differences in the manufacturer (e.g., production process, labor costs across geographies).



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Using one or more of the above, a hypothetical production process model can be developed to project costs for an early stage product taking into account both specific product and manufacturer attributes. Often, this model can serve as a starting point for capturing production costs. Adjustments based on industry knowledge and/or direct manufacturer data can then be made for differences in production process (by step), manufacturing location, scale, etc. One should also be sure to capture fully loaded costs, including indirect costs, which can be overlooked in an analog analysis.

Based on experience, the Inside-Out (and in some cases Hybrid) approach is our preferred approach as the foundation finds direct manufacturer input (and data) to be particularly helpful in any PE assessment. Analyses based on an Outside-In approach tend to be the most high-level and are therefore often less accurate, on a relative basis. The Outside-In approach is typically the method of last resort relied upon when direct data is unavailable.

Data Collection Templates

The foundation has prepared the attached Excel template to ease and standardize data collection. Instructions for completion are self-contained within the template. In general, the tabs within the Excel template align with each of the major cost categories discussed in this handbook (see links throughout).

- ! **The foundation recognizes that manufacturers may each have their own format for keeping data (e.g., formats can be dependent upon internal accounting). To the extent that data does not align with the Excel templates provided, the foundation is open to alternative forms of initial data sharing.** Ultimately, however, the foundation's intent is to leverage the data provided by the manufacturer to conduct a PE assessment using the methodology described herein.

No information provided by any one manufacturer will ever be shared with any other manufacturer or organization without explicit consent.

Please note that any manufacturer data is treated as highly confidential. No information provided by any one manufacturer will ever be shared with any other manufacturer or organization without explicit consent.

Identifying and Capturing Fully Loaded Costs

The data collection templates present costs on both an absolute cost basis and a per-dose cost basis. Capturing costs (or ultimately calculating costs) on a per-dose basis allows for comparisons between and among vaccines on a more consistent basis.

In order to calculate costs on a per-dose basis, it is important to determine the appropriate denominator, which may vary by stage. For example, the appropriate denominator for bulk production may be mass or volume, whereas for finished dosage form, it may be units or doses. Care should be given to identify the volume actually produced or expected to be produced based on operational capacity. In other words, volume should be based on **operational maximum capacity**, which takes into account planned downtime for repairs and maintenance as well as batch failures, whereas **theoretical maximum capacity** is the maximum capacity obtained if a facility operates during all operating hours and has no wastage or downtime.



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Volume for this calculation is therefore not the volume demanded by the market, the volume ultimately sold into the market, nor the manufacturer's theoretical capacity. Instead, volume is calculated as the volume actually produced, which takes into account existing process capabilities, operational constraints (e.g., yields, equipment scale, single-product vs. multi-product operation, bottlenecks, changeover time, planned downtime, wastage, etc.), and appetite for risk.

Costs may also be expressed on a per-course basis in order to establish a consistent metric for total regimen costs across vaccines used to treat the same condition but require differing dosage regimens. A course is defined as the number of doses per regimen (e.g., there may be three doses per course) and can therefore easily be calculated by multiplying costs per dose by the number of doses per course.

! Both per-dose and per-course costs should be calculated after any allocations are made such that costs are for the specified vaccine in the specific market of interest. (See the Allocations of Costs section for more detail on allocations).

Volume is calculated as the volume actually produced, which takes into account existing operational constraints.



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Determining PE Costs



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Organization of Types of Costs
Costs by Production Step
Types of Costs

Organization of Types of Costs

For the purposes of this handbook, there are different types of costs that are included in a PE assessment. These are defined in this section and discussed in detail throughout the remainder of the handbook. Note that manufacturers may have different methods of organizing costs and that the methodologies discussed below serve only to illustrate the reliable and consistent approach employed by the foundation in a PE assessment.

Costs incurred throughout the product life cycle of a vaccine can be grouped into specific cost categories. The cost categories included in this handbook are:

- Product Development;
- Facilities and Equipment;
- Direct Labor;
- Consumables;
- Overhead;
- Commercialization; and
- Licensing Costs.

Potential offsets to those costs include:

- Third-Party Contributions; and
- Foundation Contributions.

To the extent possible (and relevant), each cost category, specifically Direct Labor, Consumables, and Facilities and Equipment, should be segmented by production step. Additionally, throughput, yield, scale of operation, and operational capacity should be defined for each production step. These production steps are:

- Bulk;
- Form/Fill/Finish;
- Packaging; and
- QA/QC.

Cost categories are organized or grouped into different **cost classifications**. These cost categories are:

- Fixed;
- Variable; and
- Semi-variable.

These cost classifications reference how a given cost category is impacted by changes in volume. (Additional discussion on the impact of scale is discussed in the Impact of Economic Variables section).

Costs can also be dichotomized into direct costs and indirect costs, which differentiate costs based on whether they are solely relevant to a specific product in a specific market or are general costs that affect multiple products and/or multiple markets. (Direct and Indirect Costs are discussed further in the Allocation of Costs section).

Characterization of costs is important not only for standardization, but to understand how costs may move and change over time and at different volumes.



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Costs by Production Step

The foundation's data collection methodology as described within this handbook places an emphasis on data collection by production step, to the extent available. The desire to collect data and process information and to assess the components by production step is driven by the foundation's goal to fully understand the drivers of PE. Particularly when manufacturers have limited or no cost data for commercial manufacturing (as in the case of a development-stage vaccine), process information is especially helpful in estimating PE COGS for commercial scale production. This understanding can help shape an appropriate investment construct and can also help identify potential areas for reductions in cost, which in turn can increase affordability and sustainability.

While the foundation recognizes that manufacturers may not keep costs in a format consistent with the production steps laid out in this handbook, to the extent possible segmenting relevant cost categories by these four main production steps can allow for further insights to be made from the PE assessment.

The four primary product steps are as follows ([see details noted previously](#)):

- **Bulk**
- **Formulation, Filling, and Finishing (Form/Fill/Finish)**
- **Secondary Packaging**
- **QA/QC**

As described above, it is also helpful to capture process information, including a description of major unit operations, process equipment, scale, and overall and step yields. Certain documents commonly developed by manufacturers, such as **process flow diagrams**, bills of materials, product specifications, and equipment lists are useful for this purpose.

Segmenting relevant cost categories by the main production steps allows for further insights to be made.



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Types of Costs:

Cost Classifications and Cost Categories

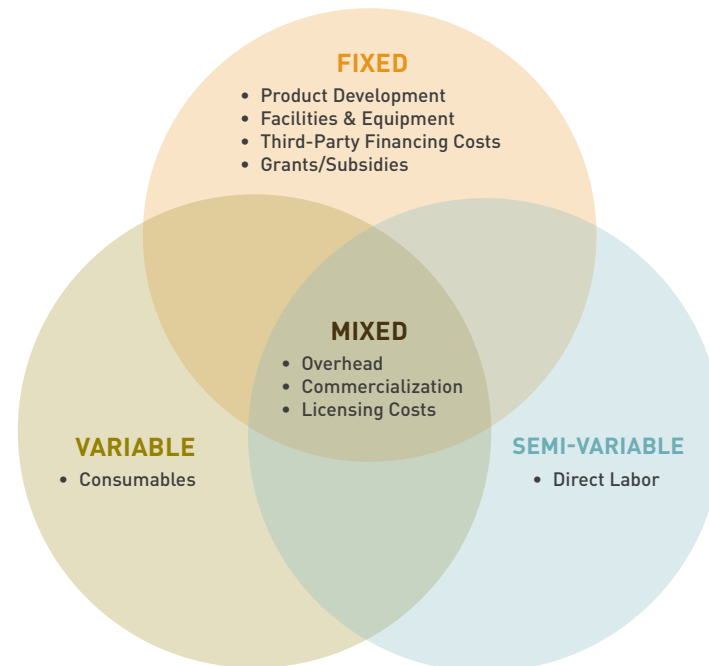
There are three broad types of costs into which the nature of the cost categories are classified: fixed, variable, and semi-variable.

- **Fixed costs** are costs that will not change as output increases or decreases and thus, by nature, will not be impacted in aggregate by changes in output. As such, per-dose fixed costs will decrease with an increase in output (up to a certain point) and vice versa, as the same total costs are being spread across a greater number of doses.
- **Variable costs** are costs that will increase directly with additional output. In other words, each additional unit produced will require additional variable costs.
- **Semi-variable costs** are costs that are correlated with output in aggregate, but not as directly as variable costs. The most common example of a semi-variable cost is direct labor, as labor costs will not increase with each additional unit of the vaccine produced in the same manner that consumables will, but the direct labor costs of production are still fairly sensitive to output.

Determining the nature of the costs included in each cost classification (i.e., fixed, variable, and semi-variable) is an important step in understanding how changes in volume will impact PE, and the impact that allocation methods will have on per-dose expenses (this point will be discussed in greater detail in the Allocation of Costs section). Note that certain cost categories (e.g., overhead) are comprised of a range of specific costs (e.g., IT systems, management) and may not fit into one cost classification. In addition, a specific cost category may have a different cost classification depending on the product and/or manufacturer.

The diagram below classifies each of the cost categories by the appropriate cost classification.

DIAGRAM 2: SAMPLE COST CATEGORIES GROUPED BY COST CLASSIFICATIONS



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Fixed Costs

PRODUCT DEVELOPMENT

► DEFINITION

Product development includes costs incurred by a manufacturer to discover, develop, and bring a vaccine to market. The two primary components of product development are **research and development (R&D)** and regulatory. Specifically, product development costs may include items such as:

- Discovery;
 - Clinical trials;
 - Animal studies, including preclinical toxicology
- CMC work, including analytical and process development, process validation, and formulation development
- R&D for national regulatory authorities (NRA);
- R&D for WHO PQ; and
- Regulatory expenses (e.g., filing fees).

Product development includes both general and product-specific items. Although all general product development costs will not be relevant to the specific product being analyzed, it is important to understand all costs a manufacturer bears and potentially make allocations of general costs as appropriate.

► GUIDELINES

To the extent that product development costs relate to multiple products and/or multiple markets, these costs should be allocated using the methods discussed in the Allocation of Costs section. For accounting purposes, product development costs are typically

expensed in the year they are incurred, rather than capitalized. However, to smooth out costs and ensure that all relevant investment costs are included (these are calculated at a particular point in time), product development costs directly related to the vaccine should be capitalized over a relevant period of time (referred to as the **useful life**) and be included through amortization. This treatment allows for product development expenses to be converted to an annual amount, which can in turn be divided by annual production volume to arrive at a per-dose cost. It is important to note that there is no standard amortization schedule, but the remaining patent life (or a reasonable proxy) of the vaccine or the remaining life of the vaccine before it is replaced by a competitor's product or new version of the same vaccine (e.g., Prevnar 13 vs. Prevnar 7) is often used as an estimate. In our experience, useful life typically ranges from 10 to 20 years. Performing sensitivities around the useful life, especially in the case that development expenses are significant, can be useful.

! To the extent all or a portion of product development costs were funded by charitable or other public sources, only costs incurred by the manufacturer will ultimately be included in the PE COGS. However, to have visibility to the full cost of product development, mechanically, total product development costs should be in this cost category and the funds provided by the charity or other public source should be included as an offsetting cost in the appropriate cost category (e.g., third-party contributions, foundation contributions). A separate template to capture product development costs can be provided by request.



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► EXAMPLE

The vaccine requires the manufacturer to employ technology and processes it does not have previous experience with, and therefore it must incur R&D costs before production can begin.

- These costs are specifically related to the vaccine and should be included in the cost base.
- If these costs relate to the vaccine, as well as other vaccines currently in production, the costs should be allocated among vaccines using an appropriate allocation key (see the Allocation of Costs section).
- If these costs were funded by a grant from the foundation, they should be included in R&D but offset in the foundation contributions cost category by a negative cost of equal magnitude.

! **Note that including both the cost of the R&D and the grant will result in a net impact of zero. However, it is useful to show both for illustrative and comparative purposes.**

FACILITIES AND EQUIPMENT

► DEFINITION

Facilities and equipment refers to the fixed assets held on the manufacturer's balance sheet and depreciated. For a vaccine manufacturer, this will include:

- Process equipment;
- Plant and critical utilities;
- Buildings;
- Land;
- Machinery and equipment;

- Furniture and fixtures;
- Office equipment; and
- Infrastructure (e.g., roads).

A manufacturer operating on a contract basis may not own the equipment and the associated expense may instead take the form of rent (typically an annual expense).

► GUIDELINES

The fully loaded cost base of a vaccine will be affected by facilities and equipment in two ways: depreciation expenses and ongoing costs of upkeep (e.g., repairs and maintenance, utilities).

► DEPRECIATION EXPENSES

Facilities and equipment expenditures are capitalized upfront, meaning that from an accounting standpoint, the costs associated with the purchases are spread over the useful life of the asset rather than being expensed entirely in the year when the purchase occurs. It is important to note that there is no standard depreciation schedule; rather, the depreciation schedule is based on factors such as the purchase price of the asset, the residual value (meaning the amount the asset could be sold for at the end of its useful life), and the expected useful life of the asset. Therefore, the depreciation schedule and useful life may differ for each of the relevant assets. Further, for inclusion in the fully loaded cost base, the appropriate depreciation schedule may differ from the accounting or tax treatment and differ within facilities and equipment. The useful life of a piece of equipment or facility is typically equal to an estimate of the duration that the equipment or facility will contribute to the business before it becomes obsolete and needs to be replaced. The useful life is typically shorter for a novel piece of equipment (e.g., a filling line) vs. a brick-and-mortar facility.



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When accounting for depreciation to determine PE COGS, it is advisable to start with the original cost of the asset, the useful life, and the depreciation schedule (e.g., straight line) to determine the annual depreciation figure in each relevant year. There may then be certain offsets to the depreciation amount to take into account: depreciation recovered on the asset during a prior use (e.g., depreciation associated with a facility that was recovered when the facility was in use previously for a different product), any grant or subsidy associated with procuring or building the asset, and any other adjustments that might be relevant, including allocations between products and/or markets as discussed in the Allocation of Costs section. To understand a comprehensive picture of an asset and its impact on Production Economics, it is helpful to detail these steps in the calculation.

► ONGOING COSTS OF UPKEEP

In addition to the capital outlay associated with building/purchasing facilities, equipment, and other assets, manufacturers incur annual operating expenses associated with the upkeep of these assets. Ongoing costs of upkeep, such as repairs and maintenance and utilities (e.g., electricity, water) should therefore also be included in this cost category. That said, these costs are annual costs and should not be capitalized.

For example, the total annual cost associated with one piece of equipment would be the annual depreciation expense plus any expenses involved with maintaining that equipment during that year.

► EXAMPLE

In order to supply a vaccine to the Gavi market, the manufacturer will build a new, dedicated \$10-million facility in 2016 that will begin operating on January 1, 2017 with a useful life of 20 years.

- For each year over the next 20 years (i.e., 2017 to 2037), a depreciation expense of \$500,000 (assuming straight-line depreciation) will be incurred and should be included in PE COGS.
- Separately, an annual expense will also be incurred and will include any costs associated with maintaining/repairing the asset over the course of a given year as well as other operational costs such as utilities.

Variable Costs

CONSUMABLES

► DEFINITION

Consumables are defined as materials used as inputs in production, including raw materials. For a vaccine, consumables include:

- Bulk consumables such as biological and chemical agents along with all raw materials and consumables used in the production of the bulk vaccine;
- Fill/Finish consumables such as vials, stoppers, and seals;
- Packaging consumables such as labels, including vaccine vial monitors (VVM), and secondary and tertiary cartons; and
- QC consumables such as inputs for testing kits.



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► GUIDELINES

Typically, consumables for each production step are related to both the manufacturing process design and the scale of operation, which should be clearly defined, particularly if different scales of operation are used in different sections of the production process. For capturing the manufacturing process design, as described above, the availability of a **process flow diagram** and **bill of materials** are particularly useful. This information should include all significant raw materials, process solutions, and process consumables (e.g., filters, chromatography resins, buffer bags) used in the manufacturing process for each production step. Process yields should also be described by unit operation or process section.

Consumables costs also include all shipping and freight costs involved with having consumables delivered, if these costs are borne by the manufacturer. Further, consumables costs will include all import taxes (such as value-added taxes).

Consumables costs should also include the cost of extra materials used up due to wastage (e.g., broken vials and overfill) or product failures. In other words, the PE assessment should account for expected normal loss rates.

Some consumables are 100 percent variable in that each additional dose produced requires additional raw material inputs. However, certain consumables are only semi-variable in that additional production will ultimately require additional raw material inputs—but this is not one for one. For example, a single disposable filter may be used to process an entire batch of a vaccine. Other consumables, such as chromatography resins, may be used for multiple batches of vaccine before their useful life is extinguished. As such, it is important to understand the variable nature of material consumables by providing information such as capacity and lifetime of the consumables where appropriate. Again, a bill of materials may be helpful for making these distinctions. Bulk antigen obtained from a

third party (as with all products obtained from third parties) should be included at cost to the manufacturer, without any additional markup.

► EXAMPLE

Due to overfill, breakage, and other types of wastage, consumables for a theoretical yield of 112 million doses are required to produce 100 million doses.

- Raw material costs per dose should be calculated based on the cost of materials necessary for 112 million doses, divided by the actual yield of 100 million doses.

Semi-Variable Costs

DIRECT LABOR

► DEFINITION

Direct labor costs are fully loaded and include all employee costs directly attributable to the production of the specific vaccine, such as:

- Wages (including overtime);
- Bonuses;
- Fringe benefits (e.g., healthcare, payroll taxes, etc.); and
- Product-specific training.

Costs will vary by product and manufacturer based on market labor rates, manufacturing labor intensity, worker skill-level required, and complexity of manufacturing processes.

Indirect labor costs are discussed below and in more detail in the Overhead subsection.



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In accounting for direct labor costs, it is useful to distinguish between direct labor and indirect labor:

- **Direct labor:** Labor costs that can be easily attributed to a specific product in a specific market. For example, the employees working on a specific vaccine are a direct cost for that product.
- **Indirect labor:** Labor costs that benefit multiple products and/or markets, and thus can only be indirectly attributed to a specific product or market. For example, the costs of a manufacturer's plant management wages are indirect costs because they apply to all products and markets produced within a given facility.

An overview of staffing levels for all GMP-related functions (i.e., through an organization chart if appropriate) as well as specific data on labor expenses by production step are both particularly helpful for this part of the analysis. If specific data on labor expenses by production step is unavailable, allocation by the time spent or headcount related to each step can be applied to estimate a proportionate division of labor expense. Product specifications, which can help define QC testing requirements, are also helpful. As mentioned previously, indirect labor costs should be accounted for in the Overhead subsection. Within Overhead, indirect labor, if it relates to plant management may be included in Indirect Overhead, whereas if it relates to C-suite executives it may be included in Corporate Overhead.

► EXAMPLE

In the first year of production, the manufacturer expects to have 40 full-time employees engaged directly in the vaccine production on a single shift basis. But as demand increases, based on the manufacturer's experience with other similar products, the manufacturer expects to switch to a multi-shift operation with 65 full-time employees to double production.

- Total direct labor costs will increase as more employees are hired to execute the multi-shift operation;
- The manufacturer's direct labor costs on a per-dose basis should decline to reflect the reduction in labor necessary as experience is gained and capacity utilization increases.

Cost Categories Spanning More Than One Type of Cost

OVERHEAD

► DEFINITION

Overhead costs are indirect costs that are necessary for the manufacturer to function, but are not directly attributable to a specific product. Overhead may include such items as:

- Indirect labor;
- Management;
- IT systems;
- Insurance;
- Transportation;
- Security; and
- Other head-office or back-office expenses.



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For the purposes of this handbook, Overhead costs are split between **Indirect Overhead** and **Corporate Overhead**. While each of these two categories may include items from the above list, the distinction made is that Indirect Overhead is associated with all indirect expenses at a specific plant, whereas Corporate Overhead is associated with all indirect expenses incurred by the manufacturer outside of the specific plant that are required to support the broader operations of the manufacturer.

► GUIDELINES

Overhead costs typically apply to many or all products made by a manufacturer; as such, overhead should be properly allocated among all products to reflect actual overhead usage rate. The allocation of Indirect Overhead and Corporate Overhead may very well be different.

Further, different individual costs within the overhead cost category fall under different cost classifications. For example, the insurance costs would be semi-variable, whereas an internal IT system would be a fixed cost.

► EXAMPLE

A manufacturer spends \$5 million annually maintaining an IT system in a plant that is used to produce five vaccines. The manufacturer believes that the associated overhead expense can be allocated evenly between the vaccines.

- Each vaccine will be allocated \$1 million of Indirect Overhead annually.
- The \$1 million can be divided by the vaccine's annual production volume to find the per-dose impact of the overhead expense.

COMMERCIALIZATION

► DEFINITION

Commercialization costs are expenses incurred post-regulatory approval such as ongoing sales and marketing costs. Specific examples may include:

- Advertising;
- Marketing materials;
- Sales force; and
- Distribution.

► GUIDELINES

Commercialization costs are often particular to specific markets; as such, it is important to only account for costs relevant to the market where the vaccine is being sold. Commercialization expenses that span multiple products or markets (such as a global, companywide ad campaign) should be properly allocated between products and markets. Note that commercialization costs will typically be low for the Gavi market where procurement is through UNICEF and marketing is not necessary. **It is not appropriate to incorporate commercialization costs incurred exclusively for high-income markets into the cost base of the vaccine intended for the Gavi market.**

Manufacturers may not account for commercialization costs separately. Do not double count with costs captured in other categories, such as indirect labor involved with marketing or sales that may be captured within Overhead.



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► EXAMPLE

The manufacturer is negotiating an agreement to supply the vaccine through UNICEF's Supply Division for procurement by several countries, including India. Additionally, the manufacturer intends to market the vaccine in certain Western markets (e.g., the United States and Europe).

- Commercialization costs for India should be minimal given the procurement method. To the extent the manufacturer conducts any additional commercialization efforts in India, costs associated with these efforts should be included. That said, in most instances this is unlikely.
- Commercialization costs for the Western markets are relevant, but should be 100 percent allocated to the Western markets and have no impact on the PE COGS for the vaccine for the Indian market or other non-Western markets.

Other Cost Categories

LICENSING COSTS

► DEFINITION

Licensing costs include any income received (or expenses paid) for granting (or licensing) the right to use product-related intellectual property (e.g., technology) in order to develop, produce, and/or commercialize the vaccine.

► GUIDELINES

Payments to third parties should be considered costs to all applicable products and should be allocated to the extent the licensed intellectual property is used across different products

and/or markets. Income received from the out-licensing of intellectual property should likewise be allocated if necessary and counted as a negative cost.

Licensing expenses can be fixed, variable, or semi-variable, depending on the payment structure. For example, a one-time payment would be amortized and counted as a fixed cost, whereas a variable payment structure based on volume could be a variable or semi-variable cost. Licensing expenses can also take the form of a royalty, meaning that the licensee will be obligated to provide the licensor a percentage of the revenue earned using the licensed technology.

► EXAMPLE

The manufacturer spends \$100 million developing a process and amortizes that process over 10 years, thus incurring a charge of \$10 million in amortization annually. However, another manufacturer pays \$5 million annually for the right to use the process.

- The \$10 million amortization expense would count as a product development cost.
- The \$5 million of income would count as licensing income and a reduction to licensing costs.

THIRD-PARTY CONTRIBUTIONS

► DEFINITION

Third-party contributions include all contributions from governments and other third-party (i.e., non-foundation) organizations. Specifically, this category includes:



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- Loans;
- Grants;
- Subsidies (e.g., government subsidies for land or other resources);
- Tax credits (e.g., for R&D and specific investments); and
- Other incentives (e.g., priority review vouchers).

Each of these items is generally an offset to PE COGS. However, third-party financing costs, which include debt payments (e.g., interest) related to specific financing obtained for the product analyzed have a cost component and should be included in PE COGS.

► GUIDELINES

Only those third-party contributions directly related to the incremental production of the vaccine being assessed should be counted. In other words, if a firm takes out debt as a way to fund its day-to-day operations, then this should not be considered to be part of the PE COGS. However, if a firm takes out a loan in order to fund capital expenditures to increase capacity, then the cost of that loan should be allocated to all products that benefit from the capital expenditure.

This section should also include all potential financing-related costs, such as the carrying costs associated with late payments and accounts receivable (e.g., from raw material manufacturers) including any ensuing financing costs as well as opportunity costs due to the time value of money borne by the manufacturer.

Since interest payments are generally fixed, financing costs are a fixed cost.

Tax credits received should be considered when quantifying the annual cost of those investments. In other words, if a manufacturer received a tax credit for building a new facility, thereby reducing its income tax payment, the cost of the facility included should

be computed as the actual cost of the facility less the tax credit. Similarly, direct government subsidies related to the product analyzed should also be taken into account. In some cases (e.g., subsidy for the purchase of land), they may need to be allocated across multiple products.

To the extent that tax credits or subsidies are related to a fixed asset, these are fixed costs (or rather, an offset to fixed costs).

A priority review voucher is a government incentive that allows a manufacturer to be able to bring the product to market relatively faster and may allow the manufacturer to generate product revenues sooner and potentially achieve a first-mover advantage. Thought should be given to if and how the benefit of the priority review voucher should be included as an offset to the costs of the product that generated the voucher.

► EXAMPLE

As a result of taking out a \$10-million loan to build its new facility, the manufacturer incurs a yearly interest expense of \$1 million.

- The initial cost of the facility would be added as a facilities and equipment cost and be counted annually through depreciation.
- The annual interest expense would be counted as a financing cost.
- The time value of money component associated with borrowing money (i.e., the benefit involved with receiving money now) should also be taken into account as an offset to the PE COGS.

India subsidizes product exports and China subsidizes electricity costs for some manufacturers.

- The full reductions in the form of the subsidy would be counted against (i.e., as negative expenses or contra expenses) the PE COGS and included in this cost category.



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FOUNDATION CONTRIBUTIONS

► DEFINITION

Foundation contributions are grants, loans, or other investments provided by the foundation to manufacturers. Foundation contributions can have the impact of reductions to costs from grants or interest expenses associated with foundation loans (plus a benefit associated with the time value of money component of the loan). The foundation is also able to provide more tailored and complex contributions to meet a manufacturer's business need. The impact of these more complex investments needs to be assessed on an individual basis.

► GUIDELINES

Foundation contributions should be accounted for in the same manner as third-party grants or third-party loans. These costs are accounted for in a separate cost category only for presentation purposes.

Foundation grants will often be directed to support a specific expenditure, such as clinical trials or construction of a new facility. If the entirety of a grant is provided upfront, the costs should be spread over the useful life of the underlying expenditure (e.g., useful life of the facility the grant is used to build). The foundation may also structure grants in other ways such as providing milestone payments linked to key development benchmarks; these situations should be reviewed on a case-by-case basis to determine whether the impact of these grants should be expensed annually (i.e., each payment affects the PE COGS of the year in which it occurs) or capitalized (e.g., summed up and spread over a useful life in a manner similar to that of an upfront grant). Typically, the grant should be treated in the same manner as the associated expense.

► EXAMPLE

The foundation provides a manufacturer with a grant to be used to perform clinical trials for a new vaccine.

- The cost of the clinical trials should be recorded as an R&D expense and amortized over an estimated useful life (e.g., length of a patent for the technology and estimated time until competitors enter market).

The annual impact of the grant should be smoothed over the same useful life and recorded as a foundation contribution offsetting the funded portion of the clinical trials.



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Allocation of Costs



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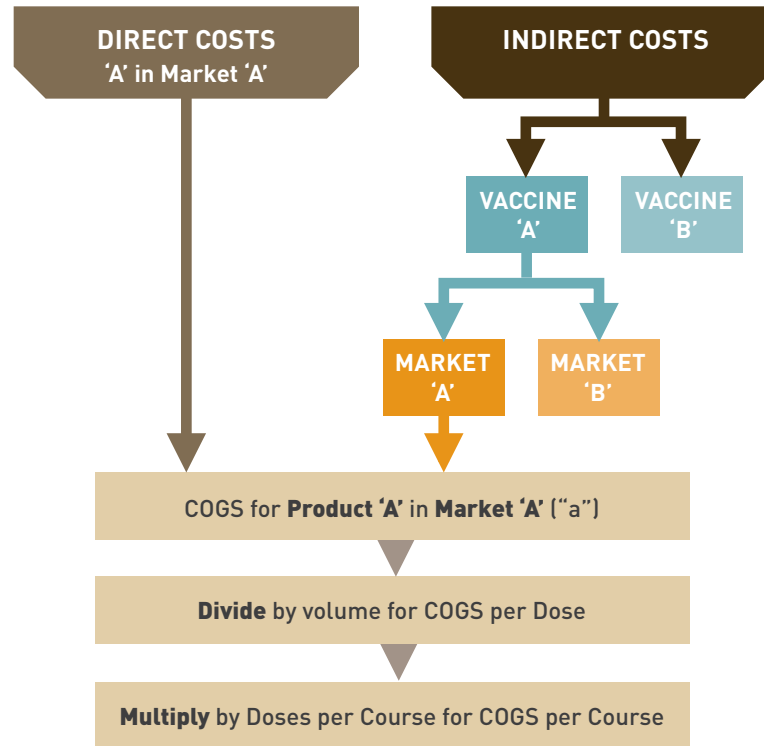
Introduction to Allocation of Costs

There are generally three reasons for allocating costs:

- To isolate the costs of resources used in the manufacture of a specific vaccine, where resources may be used to manufacture and commercialize multiple products;
- To isolate the costs of production and introduction (e.g., registration and related costs) for the vaccine specific to a particular geography when the product is sold in multiple markets; and
- To isolate production costs of a specific vaccine between production steps (i.e., bulk, form/fill/finish, packaging, QA/QC).

The diagram below illustrates how direct costs and the allocable portion of indirect costs build up for a specific product (Product 'A') in a specific market (Market 'A'), which can then be expressed on a per-dose or per-course basis. Note that in this example, indirect costs are allocated first by product and then by market; in certain instances, only one of the two will be necessary (e.g., if a manufacturer makes only one product but supplies it to multiple markets). This diagram does not include allocations by production step.

DIAGRAM 3: DIRECT COSTS AND ALLOCATION OF INDIRECT COSTS TO ASSESS PE FOR A VACCINE IN A SPECIFIC MARKET



Allocation Keys

The metric used to allocate costs is called an **allocation key** and is based on an observable characteristic of the production or sale of the vaccine.

The aim should be to select an allocation key that balances **accuracy, simplicity, and equity**, with the greatest weight placed on accuracy.

The primary allocation keys used are generally volume and revenue. However, there are many other common allocation keys (some of which are described below). Any observable characteristic could be used as an allocation key provided that it leads to a reasonably accurate apportionment of costs.

When allocating costs, it is good practice to avoid using rules of thumb that are not based on the actual production of the vaccine, and should always ensure that the allocation method employed will not lead to over-allocation of costs if applied to all of the manufacturer's products. For example, if a company allocates 30 percent of overhead costs to each of its 10 vaccine products the result would be a total allocation of 300 percent of overhead costs instead of 100 percent.

Manufacturers should provide any available data on the metrics used for the allocation keys below.

METRIC	DEFINITION	EXAMPLE
ACCURACY	The allocation key should reliably reflect the cost drivers.	If the cost of form/fill/finish is primarily driven by the amount of time it takes to fill/finish a particular vaccine, and the time it takes to fill/finish two different vaccines is approximately equal on a per-dose basis, then allocation by volume would provide a reasonable estimate of the resources used by each vaccine.
SIMPLICITY	The allocation key should be easily and inexpensively obtained.	Production volume is often readily available, whereas actual time spent by employees on particular activities may be unavailable or require an additional, and perhaps costly, analysis.
EQUITY	The allocation key should take into consideration the ability to bear the cost.	A higher margin product earning a larger return should bear a greater proportion of investment costs and indirect costs associated with production. In this way, products sold in higher-income markets may have a higher cost than (nearly) identical products sold in lower-income markets.



Overview of Common Allocation Keys

Volume Allocation

► DEFINITION

A **volume allocation** key allocates costs to different products and markets based on the relative volume produced or sold.

► EXAMPLE

100 million doses of a vaccine are produced and sold in different markets.

- 90 million doses are sold in non-Gavi markets.
- 10 million doses are sold in Gavi markets.
- Based on volume allocation, 10 percent of costs would be allocated to production for Gavi markets (i.e., $10 / (10 + 90) = 10$ percent).

A fill/finish facility with a 25-million-dose capacity is shared between two vaccines.

- 5 million doses of vaccine A are sold by the facility.
- 20 million doses of vaccine B are sold by the facility.
- Based on a volume allocation, 20 percent of costs would be allocated to vaccine A (i.e., $5 / (20 + 5) = 20$ percent).

The volume allocation key implicitly assumes that the cost to produce a single dose does not vary across products or by region.

The optimal type of allocation utilized depends on the specific scenario.

The volume allocation may also apply to costs applied to different presentations of the same vaccine (e.g., if a manufacturer produces a vaccine in a 1-dose vial for some markets and a 5-dose vial for others); in these cases, costs that are shared may be allocated by volume while costs that are specific to one market are only allocated to that market.

Note that by using a volume allocation, the benefits of economies of scale created by producing more vaccines for either market are shared across both markets.

Volume sold and volume produced are both reasonable allocation keys, but do differ. For example:

- A manufacturer may intentionally overproduce to stockpile inventory for future sale; or
- A manufacturer may experience wasted batches due to a manufacturing error.

Consideration should be made as to whether volume sold or volume produced is most appropriate in each situation.



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Revenue Allocation

► DEFINITION

A **revenue allocation** key allocates costs to different products and markets based on relative revenues.

► EXAMPLE

20 million doses of a vaccine are produced and sold in different markets.

- 10 million doses are sold in non-Gavi markets at \$9 per dose.
- 10 million doses are sold in Gavi markets at \$1 per dose.
- Based on revenue allocation, 10 percent of costs would be allocated to Gavi markets (i.e., $1 / (9 + 1) = 10$ percent).

By comparison, using a volume allocation, 50 percent of costs would be allocated to lower-income markets (i.e., $10 / (10 + 10) = 50$ percent).

Other Allocation Keys

Other allocation keys may be appropriate in apportioning costs to different products, markets, or production steps in certain circumstances.

Other examples of allocation keys that may be appropriate are:

- **Time** – Use of a bulk production facility is split between two vaccines. Every year the facility produces vaccine A for 13 weeks and vaccine B for 26 weeks, with the remaining 13 weeks necessary for transitioning the facility between vaccines. Based on a time allocation, 33 percent of costs would be allocated to vaccine A and 67 percent of costs to vaccine B;
- **Square footage** – If a building has production split between two suites, then it may be appropriate to allocate the indirect building costs based on the suites' relative square footage; and
- **Headcount** – Costs of employee benefits may be most appropriately allocated based on the number of employees engaged in a particular activity.



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Impact of Economic Variables



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Foreign Exchange Rates

Changes in Costs Due to
Volume Increases/Decreases

Economies and
Diseconomies of Scale

Capacity Constraints

Impact of Economic Variables

In order to forecast how costs may change over time, it is important to understand how costs may be affected by various economic variables, such as inflation rates, foreign exchange rates, changes in costs due to volume increases/decreases, economies and diseconomies of scale, and capacity constraints. For example, these variables are important to consider when:

- Projecting future costs of a specific vaccine (e.g., projecting 2016 costs for a PE assessment on a product that is expected to be launched in 2020, and as such the year under analysis is post-2020);
- Aggregating analog vaccines by production step to assess PE for a specific vaccine; and
- Making adjustments to financial projections of a specific vaccine to account for recent changes in scale, location, etc.

Inflation Rates

Inflation refers to the increase in prices over time, and consequently, the decrease in the purchasing power of money. For example, as prices of inputs related to the vaccine's production increase, underlying costs will increase.

Rates of inflation may differ between markets. For example, while inflation in the United States (and in U.S. dollars) is generally low (i.e., less than three percent per year), inflation in some markets exceeds 10 percent per year. Markets with developing economies, such as India, typically exhibit higher inflation rates than markets with mature economies, such as the United States.

In general, past inflation trends can serve as a useful predictor of future inflation. However, it is important to understand that inflation rates can be cyclical in nature, and it is therefore insufficient to simply extrapolate rates from the previous year. Utilizing multi-year averages is one means of smoothing the effect of business cycles on inflation. It is also important to consider recent trends and extraordinary events (e.g., recessionary and boom periods) when using historical inflation rates for forecasting purposes.

Foreign Exchange Rates

The costs of inputs (e.g., raw materials and wages) may be denominated in various currencies and/or not be the same as the currency in which the final product (i.e., the vaccine) is sold by the manufacturer. **Foreign exchange rates** between currencies fluctuate constantly, and understanding how currency movements affect a manufacturer's costs is crucial to projecting PE.

Similar to inflation, past exchange rates can be used as predictors for future trends, but due to the often cyclical nature of rates, an average over a multi-year period will serve as a more reasonable method of forecasting foreign exchange rates than a simple extrapolation based on a single-period rate.

Manufacturers that purchase input goods or services from foreign suppliers are exposed to the risk that fluctuations in exchange rates will decrease the purchasing power of their local currency and consequently increase effective costs. Some manufacturers mitigate risk by hedging against currency fluctuations, and any hedging costs should be included as part of the PE COGS under third-party contributions (e.g., financing costs).



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Foreign exchange rates will be influenced by inflation thus consideration should be made to avoid double counting as the impact of these economic variables should be looked at collectively.

It is important to keep in mind that foreign exchange rates will be influenced by inflation in the relevant countries; as such, consideration should be made to avoid double counting as the impact of these economic variables should be looked at collectively.

Changes in Costs Due to Volume Increases/Decreases

Cost curves are representations of changes in production costs as output increases or decreases. When a process-based model is built/available, it can assist in forecasting changes in PE COGS as a function of changes in scale, capacity, or utilization and to develop cost curves as a function of scale or capacity. **In assessing PE, cost curves can be used to:**

- **Help forecast changes in a manufacturer's costs based on changes in expected future output; and**
- **Compare costs at different volumes, which can inform decisions about optimal output.**

Since fixed costs are costs that will not change as output increases or decreases, they will not be impacted in aggregate by changes in output (until capacity constraints, described in detail below, are reached, requiring additional capital expenditure). As such, per-dose fixed costs will decrease with an increase in output, as the same total costs are being spread across a greater number of doses.

Variable costs will increase directly with additional output. Therefore, as output increases, the ratio of fixed costs versus variable costs as part of total costs will increasingly shift in favor of variable costs.

Semi-variable costs will also correlate with output, but not as strongly as variable costs do, as each incremental increase in volume will not trigger an equally incremental increase in aggregate semi-variable expenses.

Economies and Diseconomies of Scale

Economies of scale are cost advantages that manufacturers gain from increasing output. In other words, economies of scale will cause decreases in total costs per dose as production volume increases. The main sources of cost savings for manufacturers may include:

- Decreased raw materials costs due to bulk pricing discounts;
- Production efficiencies and experience (e.g., larger batches, less wastage, increase yield); and
- The ability to spread fixed costs over a greater number of products.

Diseconomies of scale are the converse of economies of scale and represent increases in variable costs per dose as production volume increases. Diseconomies of scale can be caused by factors including:

- Inefficiencies involved with running a larger, less focused operation; and
- Decreased operating precision leading to smaller yields.



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Capacity Constraints

Capacity constraints are factors that cause breakpoints or hurdles in a cost curve, appearing as an inflection point when the fixed costs begin to increase with scale. Inflection points can be caused by the need for additional capital expenditures (increases in fixed costs) to produce additional volume. For example, a manufacturer's costs per dose may decrease with increases in output initially; however, after a certain point, additional output may require investments in new equipment and/or additional facility space, etc. When amortized and added to the per-dose cost, this can cause an increase in the per-dose cost.

Identifying the inflection points at which manufacturers will require additional capital expenditures is important, as they represent levels of output where the manufacturer will see incremental increases in the PE COGS on a per-dose basis. While the effects of economies or diseconomies of scale cause smooth changes in costs with increases in output, capacity constraints create steps where breakpoints in output cause increases in costs.



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Defined Terms

Allocation Key: Metric used to allocate costs (e.g., time, square footage, and headcount).

Bill of Materials: An itemized listing of all raw materials and consumables used in each production step. Grade of material used, supplier, and quantities required for a given production scale are typically included.

Bulk: Costs incurred in the production of the bulk product, including both upstream and downstream processes, but before any dosage form manufacturing occurs.

Capacity Constraints: Factors that cause breakpoints or hurdles in a cost curve, appearing as an inflection point when the fixed costs begin to increase with scale.

Commercialization: Expenses incurred post-regulatory approval such as ongoing sales and marketing costs (e.g., advertising, marketing, distribution, etc.).

Consumables: Raw materials used as inputs in production for a specific vaccine.

Cost Classifications: Cost categories grouped as fixed costs, variable costs, and semi-variable costs.

Cost Curves: Representations of changes in production costs as output increases or decreases.

Direct Labor: Fully loaded employee costs (e.g., wages, benefits) directly attributable to a specific vaccine.

Diseconomies of Scale: The converse of economies of scale, these represent increases in variable costs per dose as production volume increases.

Economies of Scale: Cost advantages that manufacturers gain from increasing output.

Facilities and Equipment: Costs associated with fixed assets. Includes capitalized costs that depreciate over time (e.g., land, buildings, machinery, etc.) as well as ongoing costs of upkeep (e.g., repairs and maintenance, utilities, etc.).

Fixed Costs: Costs that will not change as output increases or decreases and thus, by nature, will not be impacted in aggregate by changes in output. As such, per-dose fixed costs will decrease with an increase in output (up to a certain point) and vice versa, as the same total costs are being spread across a greater number of doses.

Formulation, Filling, and Finishing (Form/Fill/Finish): Costs incurred during the formulation (including adjuvantation and lyophilization), filling, and finishing steps of the production process, before any secondary packaging.

Foundation Contributions: All contributions (e.g., grants, loans) from the foundation.

Hybrid: A combination of two data collection approaches generally comprised of using third-party sources to substantiate or augment data received directly from the manufacturer.

Indirect Labor: Labor costs that benefit multiple products and/or markets, and thus can only be indirectly attributed to a specific product or market (included in Overhead).

Inflation: Refers to the increase in prices over time, and consequently, the decrease in the purchasing power of money.

Inside-Out: Data collection approach based on quantitative and qualitative data, and process information received directly from the manufacturer.

Intervention Target Product Profile (iTTP): A profile established by the foundation for priority vaccines to define minimal and optimal parameters for vaccines, and thereby help guide product development investments and decisions.



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Licensing: Any income received (or expenses paid) for granting (or licensing) the right to use product-related intellectual property in order to produce the vaccine (e.g., technology).

Operational Maximum Capacity: Maximum capacity achievable when taking into account planned downtime for repairs, maintenance and batch failures.

Outside-In: Data collection approach based on using indirect sources of information such as conversations with third-party consultants/experts or applicable vaccine data and process information from other sources (e.g., industry studies).

Overhead: Indirect costs necessary for the manufacturer to function, but not directly attributable to a specific vaccine, including indirect labor (e.g., management salaries, wages, training, etc.) and other operating expenses (e.g., insurance). This category can be broken into Indirect Overhead and Corporate Overhead.

Process Flow Diagram (PFD): A schematic representation of a manufacturing process, including information about process unit operations for a production step. PFDs typically include information about in-process solutions, major process equipment, critical control parameters and tests, and production scale and yields.

Production Economics (PE): A manufacturer's fully loaded cost base for a product, from the initial costs of discovery and development through manufacturing and final packaging, with allocations made as appropriate.

Production Economics Cost of Goods Sold (PE COGS): For the purposes of this handbook, PE COGS refers to all costs associated with the definition of PE above.

QA/QC: Costs involved with quality control and quality assurance testing.

Research and Development (R&D): Costs incurred to discover, develop, and bring a vaccine to market (e.g., upfront R&D, clinical trials, regulatory approval including WHO Prequalification (WHO PQ), etc.).

Revenue Allocation: Key allocates costs to different products and markets based on relative revenues.

Secondary Packaging: Costs incurred during the packaging step, commonly referred to as secondary packaging. This will generally include activities such as putting finished vaccines into cartons and preparing them for shipment. This also includes all warehousing costs.

Semi-Variable Costs: Costs that are correlated with output in aggregate, but not as directly as variable costs.

Theoretical Maximum Capacity: The maximum capacity achievable when the facility is operated during all normal operating hours and assuming no wastage.

Third-Party Contributions: All contributions (e.g., grants, loans, subsidies) from governments and other third-party (i.e., non-foundation) organizations.

Useful Life: An estimate for the amount of time a capitalized asset (e.g., investment in a facility) will be useful.

Variable Costs: Costs that will increase directly with additional output. In other words, each additional unit produced will require additional variable costs.

Volume Allocation: Key allocates costs to different products and markets based on the relative volume produced or sold.



OVERVIEW



DATA



PE COSTS



ALLOCATIONS



IMPACT



GLOSSARY

