# Vaccines Europe Position
# on forecasting of vaccine demand in Europe

Vaccines Europe member companies are committed to the public health needs of European citizens and citizens of the world. Ensuring vaccine availability in times of increased demand and supply constraints can only be achieved by a strong industry operating in a stable environment, able to produce vaccines of the highest quality and to innovate to meet future vaccine needs. Supply and demand sides need to be in balance to ensure a healthy vaccine ecosystem. If the installed capacity is too large, the fixed cost of overcapacity increases the production cost of each vaccine dose. Conversely, supply lower than demand leads to shortages, which may impact public health. All major European vaccine manufacturers are global suppliers and have the objective to meet worldwide demand as best as possible. Therefore, long-term and accurate forecasting of worldwide vaccines demand is an important factor for the successful launch of new vaccines or securing sufficient supply of existing vaccines, especially in a complex and highly regulated environment.

Today, processes and mechanisms for manufacturers to engage with recommending bodies/payers on vaccination plans evolution and to obtain anticipated and accurate figures of future demand are limited. As a consequence, manufacturers mainly make their own assumptions on future medical needs at a global level several years in advance.

The Council Recommendation on strengthened cooperation against vaccine-preventable diseases[1] recognizes that the lack of coordinated forecast planning contributes to demand uncertainty and suggests the evaluation of developing a virtual European data warehouse on vaccine needs. In line with the Council Recommendation, the European Joint Action on Vaccination (EU-JAV) is exploring the concept for an EU data warehouse for European vaccine demand and supply (EU-JAV work package 6, task 6.2).

Vaccines Europe welcomes European initiatives that could result in an improvement of forecasting of vaccine demand, in order to minimise mismatch between supply and demand.

## Factors impacting vaccine demand

The worldwide demand for vaccines is highly unpredictable. Volatility in vaccine demand is due to an increase in global population, migrations, changes in demographics (e.g. ageing) and epidemiology, national immunization programmes, reimbursement and private market demand. Even for vaccines such as Tdap, varicella or rotavirus vaccines which have been licensed many years ago, national immunization programs are still evolving in terms of introduction of new vaccines, vaccination schedules, target populations, fluctuation of vaccine coverage rates etc. Around the world, private market demand is increasing as parents are seeking to protect their children against diseases for which vaccination is not part of national immunisation programs and coverage rates also increase with the improvement of economic conditions.

Market access processes for vaccines in the European Union (EU) are complex, heterogeneous and lengthy. As a result, estimates of median times from marketing

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018H1228(01)&from=GA

authorisation to patient access range from 2 to more than 6 years. As a matter of fact, this element contributes to demand volatility.

Peak of demand due to outbreaks either because of health authorities' efforts to combat outbreaks (e.g. Berlin measles outbreak in 2015, Tuscany meningitis outbreak in 2016/17) or because parents are wanting to protect their children following media coverage of fatal cases (e.g. Meningitis B in Spain and UK) can be another relevant contributor of volatility.

Winning or losing big tenders causes significant demand fluctuations for individual manufacturers. It is therefore difficult for manufacturers to foresee these demand changes accurately. Whereas factors like evolution of the immunization program can be addressed through dialogue and improving forecasting, the tender related volume volatility could be addressed through alternative procurement models (retail model), split tender models or regional tender models or any other mechanism avoiding volume concentration in procurement (see VE position paper "Vaccines Europe Recommendations to improve tendering practices of vaccines in European countries").

The demand at the level of each individual manufacturer is impacted by introductions of new vaccines, business decisions or stock out situations of other manufacturers producing vaccines that prevents the same disease(s). For instance, the demand at the level of a manufacturer may decrease if a competitor enters the market or decides to increase its capacity. On the contrary, unexpected increases of demand may happen if a competitor experiences a manufacturing issue or decides to reallocate its capacity to other countries (e.g. due to unsustainable conditions related to demand or price).

The main factors impacting demand and their predictability level are summarised below.

| Main factors impacting demand | Predictability level for manufacturers |
|---|---|
| Demographics evolution | High |
| Changing epidemiology incl. outbreaks & pandemics | Medium/Low |
| National Immunisation plan evolution | Medium/Low |
| Typology of market (private versus public) | High |
| Public procurement practice | Low |
| Vaccination coverage rates changes | Medium |
| Stockout of similar vaccine from other manufacturer (if any) | Low |

**Factors impacting vaccine supply**

*Vaccine production lead times and time needed to build new facilities*

Vaccines are highly technical biological products with complex and lengthy manufacturing, control and release processes. A recent review of data from the four major vaccine manufacturers operating in Europe shows that the majority of vaccines have production lead times (from the start of the production of the antigen until the release of the finished product by the manufacturer) ranging from 18 to 24 months. Complex multivalent vaccines (e.g. pertussis-containing vaccines, meningococcal vaccines, pneumococcal vaccines, and HPV vaccines) can have production lead times of more than 36 months. Only very few vaccines have slightly shorter production lead times ranging from 12 to 18 months (e.g. monovalent hepatitis B vaccines). Even for seasonal influenza vaccines, the production lead times are

close to 12 months. Due to this manufacturing complexity and long production lead times, manufacturers cannot respond quickly to unexpected changes in vaccine demand.

While there may be common equipment across platforms such as bio-reactors, purification equipment, filling and lyophilization equipment, the sequence of operations and the specific cycles for each product vary. In most cases, each product (or group of products within a product family) has its own dedicated facility and production team for the manufacturing of active ingredients. To meet limited increases in vaccine demand, production capacity can be adapted within existing facilities, for instance by improving processes or by adding resources and/or equipment. Larger increases in vaccine demand can only be met by building new facilities, which requires high upfront capital investments and takes between 5 to 10 years. For new vaccines, the decision to build production facilities has to be taken when the benefit/risk profile is still unknown (typically at the end of Phase 2). This makes an estimation of future demand highly hypothetical. There are several examples of vaccines for which the newly constructed production capacity was much too small or much too large because the product profile after Phase 3 turned out to be much more positive or negative than expected.

Visibility on vaccine demand for the next 5 years would inform manufacturers decisions related to minor to medium size investments (e.g. installation and validation of a new packaging line). Horizon scanning in the timeframe of 5 to 10 years would guide manufacturers in their decisions for major investments (e.g. new facilities for antigen production).

*Complexity of worldwide regulatory requirements*

The ever increasing and diverse regulatory requirements combined with the long lead-times for regulatory approval worldwide result in considerable challenges in planning large inventories of the same vaccine at different stages of its production in order to cover the market demand until the changes are approved:

- once the marketing authorization has been granted, multiple post-approval changes (PAC) for the manufacturing processes need to be submitted to and approved by regulators to reflect changes such as capacity and robustness increases, improvements made to the facilities, equipment and/or processes, changes in raw materials or suppliers, improvements of quality control tests, etc.;
- for global manufacturers, a single PAC may have to be submitted to more than 100 regulatory agencies worldwide;
- on average, up to 4 years are needed to get a PAC approved worldwide;
- due to the complexity of the manufacturing processes, the use of live organisms, the need for germ containment, and the long manufacturing cycles, only a single manufacturing process can be used at a time for a specific vaccine;
- until regulatory approval of a change, bridging inventories of the “prior to improvement” manufacturing process must be built to cover vaccination needs.

Increased visibility on demand combined with worldwide harmonisation of regulatory requirements and approval timelines for PAC should have a positive impact on the availability of vaccines in and outside EEA.

The main factors impacting supply and their predictability level are summarised below.

| Main factors impacting supply | Predictability level for manufacturers |
|---|---|
| Production lead times | Medium |
| Quality controls (manufacturer + NCL) | Low |
| New building facility - time | Medium |
| Demand projections at global level | Medium/Low |
| Regulatory requirements (incl.PACs) | Medium/Low |

## Vaccines Europe's position on forecasting mechanisms in EEA

Vaccines Europe is supportive of European initiatives aiming at finding mechanisms to forecast future vaccine demand. A better predictability of future demand for marketed vaccines and vaccines in development will result in lower risks related to capacity investments by manufacturers, which in turn will contribute to a stronger vaccine industry and sustainability of supply.

However, some key principles will have to be met to ensure accurate forecasts and compliance with applicable law as described below.

1. *Compliance with EU competition rules and infringement of confidentiality*

The EU competition rules enshrined in the Treaty on the functioning of the European Union[2] prohibit exchanges of confidential, strategic information between competitors, such as information relating to production capacities, sales or market shares without adequate precautions or justification.

An EU data warehouse containing information on future vaccine demand would thus violate EU competition law absent sufficient aggregation and/or anonymization of planned production and capacity for vaccines considered equivalent by authorities and produced by more than one manufacturer so as to prevent the identification of individual company information.

Vaccines Europe is also very much concerned with business confidential information of manufacturers held by public bodies being subject to freedom of information requests by third parties at EU level as well as in most EU countries. Any information on current and future capacity, production, sales or market shares is highly critical and sensitive proprietary information, and therefore any disclosure is liable to cause damage to and harm the legitimate business interest of manufacturers.

As a consequence, any initiative to increase the accuracy of vaccine demand forecasts, such as an EU data warehouse for European vaccine demand and supply data under evaluation by the EU-JAV, must ensure that vaccine manufacturers are not infringing EU competition rules and data confidentiality. Vaccines Europe's position is that manufacturers should not be required to provide any business confidential information including on current or future planned capacity and production.

2. *Purpose of an EU data warehouse: increase the accuracy of forecasts*

If an EU data warehouse containing information on future vaccine demand and supply were to be developed, stakeholders must acknowledge that although this system could increase the accuracy of supply forecasts, these will remain subject to uncertainties and unforeseen events

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2008:115:FULL&from=EN

and developments. For example, while EU authorities can estimate the demand for vaccines included in the public vaccination programs they administer, it is much more difficult to evaluate the demand for travel vaccines or for vaccines which are not part of official recommendations but available on private market.

Decisions on manufacturing capacity (for the initial manufacturing facility, its extensions, improvement or replacement) are based on manufacturer's assumptions and taken at risk. This means that there cannot be a guaranteed capacity to cover future needs in the absence of a firm commitment from authorities to purchase the forecasted number of doses at sustainable prices.

3. *Need for accurate, up-to-date and specific demand information*

Despite the limitations described above, a mechanism to forecast vaccine demand is expected to have added value provided that the information included in the system is accurate and kept up-to-date. Clear governance and communication rules should be established to guarantee that the EU data warehouse meets its objectives.

The information should also be as specific as possible (in terms of population, protection against specific serotypes, etc.) to allow manufacturers to identify whether their vaccines could cover the forecasted needs. For instance, two vaccines against a specific disease can contain different antigens and may not be considered equivalent by authorities. Additionally, given the differences in terms of national public health needs, budgets, vaccine distribution and administration systems as well as procurement practices, the vaccine needs should be described for each Member State or even at sub-national level.

In order to obtain a more accurate estimation of the vaccine demand in EEA, Vaccines Europe encourages authorities from all MSs to use a common and systematic approach based on the parameters listed in Annex.

4. *Need for continuous and regular dialogue*

The estimated vaccine needs may evolve over time. Longer-term forecasts (≥ 5 years) and forecasts for products in development are inevitably less accurate. In addition, for any vaccine, unforeseeable short- to mid-term supply disruptions may occur (temporary shutdown of facilities for maintenance, fluctuations in antigen production, batch failure or delivery delays, etc.). Thus, continued dialogue between manufacturers and authorities will be necessary. Such dialogue should also enable the warehoused data to be updated as may be appropriate.

Whatever the decision of European authorities regarding the development of a data warehouse for vaccine demand, Vaccines Europe recommends establishing a mechanism for continuous dialogue from the end of Phase 2 studies between individual manufacturers and health authorities, including National Immunization Technical Advisory Groups to better anticipate the evolution of vaccine recommendations and accurately forecast changing demand. Any product specific discussion with stakeholders will have to remain confidential.

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An industry for healthy lives

**Annex: Parameters to be considered for an accurate estimation of vaccine demand**

1. For vaccines with no anticipated change of recommendation:
   - size of the recommended target population (e.g. age cohorts, risk groups), including changes of target population (e.g. extension of target population to include pregnant women)
   - vaccination schedule, including changes in vaccination schedule (e.g. from 3+1 to 2+1, introduction of booster)
   - vaccination coverage and compliance (schedule completion) rates expected in the target population
   - anticipated knock-on effects on private vaccination (e.g. parents' decision to vaccinate older siblings outside of the recommended target group)

2. For new vaccines or introduction of new combination vaccines:
   - size of the target population
   - vaccination schedule
   - catch up strategy (e.g. no catch-up, catch up until a certain age limit, catch up cohorts step-by-step over years or in one big catch-up program)
   - targeted vaccination coverage and compliance rates
   - date of introduction and planned duration of the program

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