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# Bivalent rLP2086 (Trumenba®): Development of a well-characterized vaccine through commercialization

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ABSTRACT

The phrase "Process is the Product" is often applied to biologics, including multicomponent vaccines composed of complex components that evade complete characterization. Vaccine production processes must be defined and locked early in the development cycle to ensure consistent quality of the vaccine throughout scale-up, clinical studies, and commercialization. This approach of front-loading the development work helped facilitate the accelerated approval of the Biologic License Application for the well-characterized vaccine bivalent rLP2086 (Trumenba®, Pfizer Inc) in 2014 under Breakthrough Therapy Designation. Bivalent rLP2086 contains two rLP2086 antigens and is licensed for the prevention of meningococcal meningitis disease caused by *Neisseria meningitidis* serogroup B in individuals 10–25 years of age in the United States. This paper discusses the development of the manufacturing process of the two antigens for the purpose of making it amenable to any manufacturing facility. For the journey to commercialization, the operating model used to manage this highly accelerated program led to a framework that ensured "right the first time" execution, robust process characterization, and proactive process monitoring. This framework enabled quick problem identification and proactive resolutions, resulting in a robust control strategy for the commercial process.

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## 1. Introduction

*Neisseria meningitidis* (Nm) is a bacterial pathogen that causes disease solely in humans. Nm is categorized by its capsular polysaccharides into 12 serogroups, 6 of which cause the majority of disease [1]. Four of the serogroups (A,C,Y,$W_{135}$) can be controlled with capsular polysaccharide-based vaccines, but this approach is impractical for *N meningitidis* serogroup B (NmB), because the serogroup B capsular polysaccharide elicits low immunogenicity [2,3] and is similar to structures found on human neuronal cells [4]. This paper discusses the development of the first prophylactic vaccine, bivalent rLP2086 (Trumenba®, Pfizer Inc), approved in the United States against serogroup B strains. The protein antigens for this vaccine are composed of lipoprotein 2086, a surface exposed and immunogenic neisserial outer-membrane protein expressed in a vast majority of, if not all, meningococcal serogroup B strains [5–7].

Encouraging data from a Phase 1 clinical study in healthy toddlers led to the evaluation of the capability of the manufacturing process to enable the necessary acceleration to support product licensure [8]. Based on Pfizer's integrated operating model for vaccine development, the process was assessed for scalability and transferability to any manufacturing site (external or internal).

*Abbreviations:* DOE, design of experiments; DS, drug substance; ELISA, enzyme-linked immunosorbent assay; FDA, US Food and Drug Administration; FHbp, factor H binding protein; HCP, host cell proteins; NmB, *Neisseria meningitidis* serogroup B; Nm, *Neisseria meningitidis*; RPH, relevant process history; RP-HPLC, reversed-phase high-performance liquid chromatography; UFDF, ultrafiltration and diafiltration; WC, worst case.

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The process was initially deemed unscalable and difficult to transfer, and several gaps were identified that would affect the robustness of the original early-phase process. This paper discusses the approach taken to develop a robust, scalable, and transferable process and uses case studies to highlight several categories of challenges encountered along the way.

## 2. Approach to vaccine development

Most prophylactic vaccines are administered to a large number of healthy individuals who range in age from infancy to the elderly. Additionally, vaccines are licensed based on their ability to induce immune responses, and small changes in vaccine composition may result in a change in the vaccine efficacy. The combination of these two factors makes for exceptionally stringent regulatory expectations for licensure. Vaccine candidates, therefore, involve greater early investment and upfront development work than typical biologics. For example, US vaccine licensure by the US Food and Drug Administration (FDA) advises a clinical trial to demonstrate manufacturing consistency (i.e., clinical proof of lot consistency) using a minimum of three preferably full scale batches manufactured consecutively at the intended commercial facility [9]. Notably, the FDA has accepted studies using two pilot scale batches and one commercial scale batch on a case-by-case basis, but the general requirement of three batches compels companies to invest much earlier in a manufacturing site for a Phase 3 production and potential launch facility. Similar expectations are also articulated by other agencies such as the European Medicines Agency [10] and the World Health Organization [11].

From a regulatory perspective, most commercial prophylactic vaccines are not "well-characterized biologics" either because they are inherently complex or because their mechanism of action is not well understood. Sponsors must therefore initiate extensive process characterization studies and lock the production processes early in the clinical development program to ensure consistency in product quality. Failure to perform these steps may necessitate the initiation or repetition of additional clinical trials to demonstrate that significant process changes do not affect the safety and immunogenicity profile of the post-change product.

Vaccine multivalency adds additional complexity to many vaccines, including bivalent rLP2086. Pfizer's 13-valent pneumococcal conjugate vaccine, PCV13 (Prevnar 13®), which is composed of 13 different polysaccharide conjugates, is one of the most complex examples of a biologic. Manufacturing this vaccine involves 13 different fermentation, purification, and conjugation trains for the polysaccharides and one fermentation-purification train for the carrier protein $CRM_{197}$ [12]. The program of PCV13 underscores the value of developing processes that are similar between antigens for ease of manufacturability and facility fit. For example, moving from 7-valent pneumococcal conjugate vaccine (PCV7, Prevnar®) to PCV13 added the process challenge of fitting the production process for the new serotypes into an existing commercial facility. The operating model used for Pfizer's vaccine development had project milestones ensuring timely completion of requisite deliverables as the project moved between stages. These helped ensure that the project was delivering the necessary prerequisites to move to the next milestone and also ensured that the development was built on the learnings and best practices of earlier programs toward a robust control strategy for Biologics License Application filing and commercial readiness.

As stated earlier, for the case of bivalent rLP2086, the key deliverable for fast acceleration to licensure was to front-load the development and characterization work, effectively locking the process at pilot scale with minimal changes during scale-up, clinical trial material production, process validation, and commercial production. This also meant completing process characterization work during early stages of the scale-up process to commercial scale, which was 20-fold greater than pilot scale.

## 3. Bivalent rLP2086: A well-characterized bivalent vaccine

Bivalent rLP2086 is composed of recombinant lipidated factor H binding protein (fHbp) variants (one each from subfamily A and subfamily B). Amino acid sequences for the subfamily A and subfamily B variants show approximately 60–75% sequence homology between subfamilies, whereas pairwise identity within a subfamily ranges from 83–99% [6,13]. The presence of the lipid moiety on lipoprotein/lipopeptide vaccine antigens results in enhanced antibody responses [14,15] that likely contribute to vaccine coverage across serogroup B, and a previous study demonstrated the importance of lipids for fHbp immunogenicity in particular [6].

The structures of the two antigens have been well characterized [16]. Fig. 1 depicts the well-characterized lipid isoform profile, which was determined by reversed-phase high-performance liquid chromatography (RP-HPLC), for each of the antigens. fHbp contains an expected amino acid sequence that is modified with three fatty acid chains, one connected via an N-acyl linkage to the N-terminal cysteine residue and two via an O-acyl linkage to hydroxyl groups of glycerol, thioether-linked to the side chain of the N-terminal cysteine. Both variants share a consistent lipidation profile that is composed of major (1, 2, and 3) and minor lipidated (A–E) species. The N-acyl linked fatty acid corresponds to the C16:0 structure in all NmB rLP2086 lipoprotein isoforms. C16:0 is also one of the two O-acyl linked fatty acids in the three major isoforms, 1, 2, and 3. The remaining O-acyl linked fatty acids in major isoforms correspond to C16:1, C17, and C18:1, respectively. Minor and trace level lipoprotein isoforms all contain similar fatty acids, with the chain length ranging from 14 to 19 carbons [16]. Since the major species constitute 95% of the total area, the lipid isoform profile was tracked during development by the relative ratios of the major species (peak 1: peak 2: peak 3). This profile is controlled during the fermentation process and is well understood (see Case Study 1).

## 4. Process development

### 4.1. Technical challenges

Since the site selection of the commercial scale manufacturing was not finalized during development, the challenge posed for redeveloping the early-phase process was the design of a process amenable to transfer into any manufacturing facility supporting microbial fermentation. Table 1 summarizes various non-scalable issues that required resolution during the early-phase process. Modifications to the fermentation, recovery, and purification processes were incorporated to address drug substance productivity and quality attributes, process robustness, and ultimately large scale manufacturability required to meet both clinical and projected commercial requirements. Higher cell densities were achieved during fermentation by implementing a fed-batch feed strategy, where additional glucose was fed after the exhaustion of the initial glucose charge. Coupled with a modified induction scheme, this strategy improved productivity by roughly 2- to 4-fold. Significant changes to the recovery stage included use of scalable equipment, chemically defined raw materials, and unit operations routinely used in a recovery process train for a microbial fermentation. Modifications to the purification stage addressed low yield and loss of column life resulting from continuous impurity precipitation that caused product co-precipitation, operational complexity due to peak fractionation, and variable final ultrafiltration and diafiltration (UFDF) operation for consistent surfactant

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