STUDI LITERATUR PRODUKSI VAKSIN, TINGKAT EFEKTIFITAS DAN EFIKASI *PLATFORM* SUB UNIT PROTEIN DARI VIRUS *SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS* 2 (SARS-COV 2)

SKRIPSI

SITI SHYNTIANA NURROHMAHWATI
A182028

SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2022

STUDI LITERATUR PRODUKSI VAKSIN, TINGKAT EFEKTIFITAS DAN EFIKASI *PLATFORM* SUB UNIT PROTEIN DARI VIRUS *SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS* 2 (SARS-COV 2)

SKRIPSI

Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

SITI SHYNTIANA NURROHMAHWATI
A182028

SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2022

PRODUKSI VAKSIN, TINGKAT EFEKTIFITAS DAN EFIKASI *PLATFORM* SUB UNIT PROTEIN DARI VIRUS *SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS* 2 (SARS-COV 2)
LEMBAR PENGESAHAN

SITI SHYNTIANA NURROHMAHWATI
A182028

Oktober 2022

Disetujui oleh :

Pembimbing	Pembimbing
Dr.Erman Tritama. M.Si	Irma Mardiah, M.Si

KUTIPAN

Kutipan atau saduran baik sebagian ataupun seluruh naskah, harus menyebut nama pengarang dan sumber aslinya, yaitu Sekolah Tinggi Farmasi Indonesia

PERSEMBAHAN

Skripsi ini kupersembahkan untuk bapak saya Udus Mulyana dan ibu saya Siti Umaemah yang selalu memberikan dukungan moril maupun materil dan selalu mendoakan disetiap malamnya untuk keberhasilanku dan mengalirkan kasih sayang yang begitu luar biasa.

ABSTRAK

Vaksin dari *platform* subunit protein Covid-19 adalah vaksin yang zat aktif nya menggunakan bagian protein patogen yang spesifik (antigen). Sudah banyak vaksin *platform* subunit protein dari berbagai negara namun informasi mengenai produsen, *drug substance, drug product,* tingkat keefektifitasan dan efikasi dari *platform* subunit protein ini belum banyak diketahui. Studi literatur ini bertujuan untuk memberikan informasi mengenai produksi dan status produk vaksin, *drug substance, drug product* serta hasil keefektifitasan dan efikasi dari vaksin subunit protein Covid-19. Metode yang digunakan dalam studi literatur ini adalah kriteria inklusi dengan tinjauan penelitian dan artikel literatur yang berkaitan dengan produksi, *drug substance* dan hasil uji klinis yang terkandung dalam vaksin *platform* subunit protein Covid-19 dan kriteria eksklusi dengan teknologi produksi vaksin *platform* subunit protein non covid-19 dan teknologi produksi vaksin covid-19 non *platform* subunit protein. Berdasarkan hasil studi literatur *platform* subunit protein vaksin yang diproduksi oleh *Coalition For Epidemic Preparedness Innovations* (CEPI), *Finlay Institut* Iran dan Anhui Zhifei. Dengan semua status produk ditahap uji klinis fase III. Vaksin yang sudah mendapatkan izin edar diantaranya vaksin Novavax, vaksin FINLAY-FR-1 dan vaksin Zifivax. Sebagian besar *drug substance* yang digunakan yaitu protein spike RBD dan *adjuvant* aluminium dengan metode produksi DNA rekombinan. Hasil efektifitas dan efikasi masing-masing vaksin terhadap virus SARS-CoV-2 yaitu Novavax 90,4%, FINLAY-FR-1 92% dan Zifivax 81,76% .

.

Kata Kunci: *Drug substance, Drug product,* status vaksin

ABSTRACT

The vaccine from the Covid-19 protein subunit platform is a vaccine whose active substance uses a specific part of the pathogenic protein (antigen). There have been many protein subunit platform vaccines from various countries but information about the producer, drug substance, drug product, level of effectiveness and efficacy of this protein subunit platform is not widely known. This literature study aims to provide information on the production and status of vaccine products, drug substances, drug products and the effectiveness and efficacy of the Covid-19 protein subunit vaccine. The method used in this literature study is inclusion criteria with a review of research and literature articles related to production, drug substance and clinical test results contained in the Covid-19 protein subunit platform vaccine and exclusion criteria with non-covid-19 protein subunit platform vaccine production technology. 19 and non-platform protein subunit Covid-19 vaccine production technology. Based on the results of a literature study of the vaccine protein subunit platform produced by the Coalition For Epidemic Preparedness Innovations (CEPI), Iran's Finlay Institute and Anhui Zhifei. With all product status in phase III clinical trials. Vaccines that have received marketing authorization include Novavax vaccine, FINLAY-FR-1 vaccine and Zifivax vaccine. Most of the drug substances used are spike protein RBD and aluminum adjuvant with recombinant DNA production method. The results of the effectiveness and efficacy of each vaccine against the SARS-CoV-2 virus were Novavax 90.4%, FINLAY-FR-1 92% and Zifivax 81.76%.

.

Keywords: *Drug substance, Drug product, vaccine status*

KATA PENGANTAR

Bismillahirrahmanirrahim

Puji dan syukur penulis panjatkan kehadirat Allah SWT atas segala rahmat dan ridho-nya. Penulis dapat menyelesaikan penelitian dan penulisan skripsi yang berjudul **" Studi Literatur Produksi Vaksin, Tingkat Efektifitas Dan Efikasi *Platform* Sub Unit Protein Dari Virus *Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov 2)* "** dibawah bimbingan Dr.Erman Tritama. M.Si dan Irma Mardiah, M.Si.

Penelitian dan penulisan skripsi ini dilakukan untuk memenuhi salah satu syarat untuk memperoleh gelar Sarjana Farmasi di Sekolah Tinggi Farmasi Indonesia.

Penulis mengucapkan terima kasih kepada semua pihak yang telah memberikan dukungan dan arahan dalam proses menyelesaikan penelitian dan penulisan skripsi ini yaitu kepada :

1. Dr. Apt. Adang Firmansyah, M.Si. selaku Ketua Sekolah Tinggi Farmasi Indonesia,
2. Dr.Erman Tritama, M.Si dan Irma Mardiah, M.Si., selaku pembimbing penelitian,
3. Dr. apt. Diki Prayugo W., M.Si., selaku Wakil Ketua I Bidang Akademik Sekolah Tinggi Farmasi Indonesia,
4. Dr. apt. Wiwin Winigasih, M.Si., selaku Kepala Program Studi
5. Syarif Hamdani, M.Si. selaku dosen wali,
6. Seluruh staf dosen, staf administrasi serta karyawan Sekolah Tinggi Farmasi Indonesia,
7. Kepada kedua orang tau, Bapak Udus Mulyana dan Ibu Siti Umaemah yang selalu mendoakan dan memberikan kasih sayang serta dukungan dalam menyelesaikan skripisi saya dengan penuh perjuangan, saya berharap bapak ibu selalu dilindungi Allah SWT,

8. Serta teman-teman angkatan 2018 dan semua pihak yang telah memberikan inspirasi dan dukungan selama penelitian dan penyusunan skripsi ini baik secara langsung ataupun tidak langsung.

Penulis menyadari bahwa penelitian dan penulisan skripsi ini masih banyak kekurangan dan jauh dari kata sempurna karena pengetahuan yang masih terbatas. Oleh karena itu, kritik dan saran yang membangun untuk perbaikan dimasa yang akan datang. Penulis berharap penelitian dan penulisan ini dapat bermanfaat bagi penulis sendiri dan bagi pihak lain yang berkepentingan.

Bandung, Oktober 2022

Penulis

DAFTAR ISI

DAFTAR TABEL

Tabel Halaman

DAFTAR GAMBAR

Gambar Halaman

DAFTAR LAMPIRAN

Lampiran Halaman

DAFTAR PUSTAKA

Amer H, Alqahtani AS, Alaklobi F, Altayeb J, Memish ZA. 2018. Paparan pekerja kesehatan terhadap coronavirus sindrom pernapasan Timur Tengah (MERS-CoV): revisi strategi skrining sangat dibutuhkan. *Int J Menginfeksi Dis* 71:113–116

Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. 2020. *The proximal origin of SARS-CoV-2.* P. (4):450–2. https://doi.org/10.1038/s41591- 020-0820-9.

Ayittey, C. Dzuvor, M.K. Ayittey, N.B. Chiwero, A. Habib, 2020. *Updates on Wuhan 2019 novel coronavirus epidemic, J. Med. Virol.*

Bruce Alberts, et al. 2002. *Molecular biology of the cell, Most Antigens Activate Many Different Lymphocyte Clones*". Inggris, *Diakses 05-11-2002*.

Bruce Alberts, et al. 2002. *"Molecular biology of the cell, glossary. Antigenic determinant*". inggris *Diakses* 11-05-2022.

C. Colovos, T.O. Yeates. 1993. *Verification of protein structures: patterns of nonbonded atomic interactions*, Protein Sci. 2 1511–1519.

Cheung, I.F. Hung, P.P. Chan, K. Lung, E. Tso, R. Liu, Y. Ng, M.Y. Chu, T. W. Chung, A.R. Tam, 2020. *Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis*, Gastroenterology 159

Cohen AA, Gnanapragasam PNP, Lee YE, Hoffman PR, Ou S, Kakutani LM, et al. 2021. *Mosaic nanoparticles elicit cross-reactive immune responses to zoonotic coronaviruses in mice.*. P. 371(6530):735–41. https://doi.org/ 10.1126/science:abf6840.

Corum, Jonathan; Zimmer, Carl. 2021. "*How the Novavax Vaccine Works"*. *The New York Times* . ISSN 0362-4331

De Campos-Lima PO, Levitsky V, Brooks J, et al. 1994. "*T cell responses and virus evolution: loss of HLA A11-restricted CTL epitopes in Epstein-Barr virus isolates from highly A11-positive populations by selective mutation of anchor residues*". *J. Exp. Med.* **179** (4): 1297–305. doi:10.1084/jem.179.4.1297. PMC 2191457. PMID 7511684.

De Wit E, van Doremalen N, Falzarano D, Munster VJ. 2020. *SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol.* 2016;14(8):523-34.

Goernmet of Canada, 2022. *Covid-19 proteon subunit vaccines.* https://www.canada.ca/en/health-canada/services/drugs-health-products /covid19-industry/drugs-vaccines-treatments/vaccines/protein-subunit.html .

Greaney AJ, Starr TN, Gilchuk P, Zost SJ, Binshtein E, Loes AN, et al. 2021. *Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition.* P. 29(1):44–57.e9. https:// doi.org/10.1016/j.chom.2020.11.007.

Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. 2021. *SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative healthcare workers in England: a large, multicentre, prospective cohort study (SIREN).* P. 397(10283) : 1459–69. https://doi.org/10.1016/S0140- 6736 (21) 00675-9.

Hsieha , Wang-Da Liua , Yu-Shan Huanga , Yi-Jiun Linb , Erh-Fang Hsiehb , Wei-Cheng Lianb , Charles Chenb,c , Robert Janssend , Shin-Ru Shihe , Chung-Guei Huange,f , I-Chen Taib, , Shan-Chwen Changa, 2021. *Safety and immunogenicity of a Recombinant Stabilized Prefusion SARSCoV-2 Spike Protein Vaccine (MVC-COV1901) Adjuvanted with CpG 1018 and Aluminum Hydroxide in healthy adults: A Phase 1, doseescalation study.* EClinicalMedicine 38 (2021) 100989

Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, 2020. *Clinical features of patients infected with 2019 novel coronavirus in* Wuhan, China, Lancet.

Hoffmann M, Kleine-Weber H, Pöhlmann S.2020. *A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells.* P. (4):779–784.e5. https://doi.org/10.1016/j.molcel.2020.04.022.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. 2020. *SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor.* P. 181(2):271–280.e8.https://doi. org/10.1016/j.cell.2020.02.052.

Jaimes JA, André NM, Chappie JS, Millet JK, Whittaker GR 2020. *Phylogenetic analysis and structural modeling of SARS-CoV-2 spike protein reveals an evolutionary distinct and proteolytically sensitive activation loop.* J Mol p. 432(10):3309–25. https://doi.org/10.1016/j.jmb.2020.04.009.

Johnson BA, Xie X, Bailey AL, Kalveram B, Lokugamage KG, Muruato A, et al. 2021. *Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis.* P. 591(7849):293–9. https://doi.org/10.1038/s41586-021-03237-4.

Krammer F. 2020. *SARS-CoV-2 vaccines in development.* P. 586 (7830):516–27. https://doi.org/10.1038/s41586-020-2798-3.

Li X, Geng M, Peng Y, Meng L, Lu S. 2020. *Molecular immune pathogenesis and diagnosis of* covid-19. *J Pharm Anal*. published online March 5. DOI: 10.1016/j.jpha.

Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J.2021. *The reproductive number of covid-19 is higher compared to SARS coronavirus*. *J Travel Med*

Mor V, Gutman R, Yang X, White EM, McConeghy KW, Feifer RA, et al. 2021. *Short term impact of nursing home SARS-CoV-2 vaccinations on new infections, hospitalizations, and deaths.* P. https://doi.org/10.1111/ jgs.17176

Muik A, Wallisch A-K, Sänger B, Swanson KA, Mühl J, Chen W, et al. 2021. *Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. Science.* P. 371(6534):1152–3. https://doi.org/10.1126/science:abg6105

Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. 2020. *Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV*. P. 11(1). https://doi.org/10.1038/s41467-020-15562-9.

Peraturan Menteri Kesehatan Nomor 42 Tahun 2013

Piccoli L, Park Y-J, Tortorici MA, Czudnochowski N, Walls AC, Beltramello M, et al. 2020. *Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology*. P.183(4):1024–1042.e21. https://doi.org/10.1016/j.cell.2020.09.037.

Planas D, Bruel T, Grzelak L, Guivel-Benhassine F, Staropoli I, Porrot F, et al. 2021. *Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to*

neutralizing antibodies. Nat Med 2021:1–8. https://doi.org/10.1038/s41591-021-01318-5.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. 2020. *Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine.* P. 383 (27):2603–15. https://doi.org/10.1056/NEJMoa2034577

Protalix ltd dan Pfizer Inc, 2015. *Amended And Restated Exckusive License and SupplyArgeement* https://www.lawinsider.com/contracts/9NTXXVvP9BH# *drug-substance* link diakses 04 okober 2022.

R.A. Laskowski, J.A.C. Rullmann, M.W. MacArthur, R. Kaptein, J.M. Thornton, AQUA and PROCHECK-NMR: *programs for checking the quality of protein structures solved by* NMR, J. Biomol. NMR 8 (1996) 477–486.

Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. 2021 Covid-19 *vaccine BNT162b1 elicits human antibody and TH1 T cell responses.Nature* 2020;586(7830):594–9. https://doi.org/10.1038/s41586-020-2814-7.

Sasaki M, Uemura K, Sato A, Toba S, Sanaki T, Maenaka K, et al. 2021. *SARS-CoV-2 variants with mutations at the S1/S2 cleavage site are generated in vitro during propagation in TMPRSS2-deficient cells.* P. 17(1): e1009233. https://doi.org/10.1371/journal.ppat.1009233.

Simmons G, Reeves JD, Rennekamp AJ, Amberg SM, Piefer AJ, Bates P. 2004.*Characterization of severe acute respiratory syndromeassociated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. Proc Natl Acad Sci U S A.* 2004;101(12):4240-5

Tahir ul Qamar M, Shahid F, Aslam S. 2020. Vaksinasi terbalik membantu merancang vaksin subunit berbasis multiepitop terhadap SARS-CoV-2. Menginfeksi Kemiskinan

Tavares, G. Mahadeshwar, H. Wan, N.C. Huston, A.M. Pyle, 2020. *The global and local distribution of RNA structure throughout the SARS-CoV-2 genome, J. Virol.*

Toto, S. Ma, F. Malagrino, ` L. Visconti, L. Pagano, K. Stromgaard, S. Gianni, 2020. *Comparing the binding properties of peptides mimicking the Envelope protein of SARS-CoV and SARS-CoV-2 to the PDZ domain of the tight junction-associated PALS1 protein, Protein Sci..*

Unnikrishnan M, Rappuoli R, Serruto D. 2012. *Recombinant bacterial vaccines. Current Opinion in Immunology*.P. 24:337–342

Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. 2020. *Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein*. P. 183 (6):1735. https://doi.org/10.1016/j.cell.2020.11.032

WHO, 2022. Pandemi penyakit coronavirus (covid-19) https://www.who.int /emergencies/diseases/novel (Diakses 23 Februari 2022)

WHO, 2022. *Vaccine Safety Basics*. https://vaccine-safety-training.org/subunit-vaccines.html

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. 2020. *CryoEM structure of the 2019-nCoV spike in the prefusion conformation. Science* . P. 367(6483):1260–3. https://doi.org/10.1126/science:abb2507.

Xie X, Liu Y, Liu J, Zhang X, Zou J, Fontes-Garfias CR, et al. 2021. *Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera*. P. 27(4):620–1. https://doi.org/10.1038/ s41591-021-01270-4.

Yang J, Wang W, Chen Z, Lu S, Yang F, Bi Z, et al. 2020. *A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity*. P. 586 (7830):572–7. https://doi.org/10.1038/s41586-020-2599-8.

Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. 2020. *Angiotensinconverting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med*. DOI: 10.1007/s00134-020-05985-9

Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. 2020. *A pneumonia outbreak associated with a new coronavirus of probable bat origin*. P. 579(7798):270–3. https://doi.org/10.1038/s41586-020-2012-7.

Zhu FC, Li YH, Guan XH, et al. *Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial*. Lancet 2020;395:1845–54 Available fromhttps://doi.org/. doi:10.1016/S0140-6736(20)31208-3.

Z. Miao, A. Tidu, G. Eriani, F. Martin 2020. Secondary structure of the SARS-CoV-2 5'- UTR, RNA Biol.