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ACCELERATING AND INTENSIFYING MANUFACTURING TO ENABLE LARGE-SCALE SUPPLY OF A NEW ADENOVIRUS-VECTORED VACCINE WITHIN 100 DAYS

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The Coalition for Epidemic Preparedness Innovations' '100-day mission' aspires to launch of a new vaccine within 100 days of pathogen identification. We have previously reported a simple fed batch process and strategy of internationally-distributed manufacturing, which enabled 2 billion doses of the 'Oxford / AstraZeneca' adenovirus-vectored COVID-19 vaccine to be produced in less than 600 days from publication of the SARS-CoV-2 genome sequence. The majority was made and used in low and middle income countries. Here, after briefly reviewing that previous work, we will describe efforts to further improve adenovirus manufacturing for response to future pathogen outbreaks and variants.

We will outline a rapid viral seed expansion workflow suitable for the '100-day mission', allowing vaccine release to trials within 60 days of pathogen sequencing and large-scale vaccine release in a further 40 days.
We also describe a new perfusion-based upstream production process, designed to maximize output while retaining simplicity and suitability for existing manufacturing facilities. This will include description of use of new scaledown models of perfusion culture using alternating-tangential flow filtration. The Ambr250 HT Perfusion system (Sartorius) enabled multi-parallel comparison of perfusion conditions in stirred tank reactors, using a design of experiments approach. XCell Lab technology (Repligen) provided an accurate model, at 3L scale, of perfusion filter conditions suitable for use at 2000L scale. The resulting process improves upstream volumetric productivity of ChAdOx1 nCoV-19 by around four-fold and remains compatible with the existing downstream process, yielding drug substance sufficient for 10000 doses from each liter of bioreactor capacity. Techno-economic modelling suggests that, if linear scale-up were achieved, a single cleanroom containing two 2000 L bioreactors running our new perfusion-based process could supply bulk drug substance for around 120 million doses each month, costing <0.20 EUR/dose. We estimate that a manufacturing network with 32000 L of bioreactor capacity could release around 1 billion doses of a new vaccine within 130 days of genomic sequencing of a new pathogen.

This accelerated manufacturing process, along with other advantages such as thermal stability, supports the ongoing value of adenovirus-vectored vaccines as a rapidly adaptable and deployable platform for emergency response. We hope also to discuss ongoing work to achieve even greater drug substance manufacturing productivity and drug product stability.