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Review

International Nonproprietary Names (INN) for novel vaccine substances: A matter of safety

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ABSTRACT

International Nonproprietary Names (INN) are assigned by the World Health Organization (WHO) to pharmaceutical substances to ensure global recognition by a unique name. INN facilitate safe prescribing through naming consistency, efficient communication and exchange of information, transnational access and pharmacovigilance of medicinal products. Traditional vaccines such as inactivated or live-attenuated vaccines have not been assigned INN and provision of a general name falls within the scope of the WHO Expert Committee on Biological Standardization (ECBS). However, novel vaccines that contain well-defined active ingredients such as nucleic acids or recombinant proteins fulfil the criteria to be assigned INN. In the current environment where multiple SARS-CoV-2 vaccines are being developed to combat the COVID-19 pandemic and with virus variants emerging, assigning INN to well-defined vaccine substances will strengthen pharmacovigilance and ultimately enhance the safety of vaccine recipients. This article examines the background to INN for vaccines and explains the applicability and value of assigning INN to novel well-defined vaccines.

Contents

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1. Introduction

A WHO International Nonproprietary Name (INN) is a globally unique and distinct name given to pharmaceutical substances or active pharmaceutical ingredients [1]. INN improve safe prescribing, good pharmacovigilance practice and worldwide recognition of medicinal products. They are assigned to the active drug substance, not to the final drug product, and thus are distinct from the commercial or trade name given by the manufacturer to the formulated medicine, which can vary worldwide from region to region. Distinct INN can, however, contain common features. In order to group drug substances according to their molecular features or their pharmacological mode of action, the active drug substance is typically assigned a common suffix or stem with individual INN being made distinct by a unique and random prefix. INN are also valuable in medicine and pharmacy teaching programmes and a virtual School of INN has been established [2 3].

INN are obtained through a defined and regulated process of the WHO INN Programme and are assigned by the WHO INN Expert Group following a broad consultative process. The Programme was initiated in 1950 by World Health Assembly Resolution WHA3.11 and began operating in 1953 [3]. In principle, INN are assigned only to well-defined pharmaceutical substances and not to mixtures, heterogeneous or uncharacterized drugs. Thus, for many decades, INN were assigned primarily to synthetic chemical drug substances that can be well defined on a structural basis. However, even from the start of the Programme, INN were given to a few, naturally occurring, less well-defined entities such as insulin and antibiotics. With the advent of recombinant DNA technology for the development and manufacture of proteins, the naming of more complex biological medicines accelerated. The first recombinant protein to be given an INN was recombinant insulin and this was followed by naming therapeutic monoclonal antibodies and many other recombinant therapeutic proteins. Today, INN are being assigned to increasingly complex therapeutic substances such as the active ingredients of gene and cell therapy [4]. They are also assigned to the active substances of DNA, RNA, recombinant protein, recombinant virus and peptide vaccines as highlighted recently [5].

2. Vaccines, blood products and transplantation substances

Some medicinal substances have remained outside the remit of the INN naming scheme such as traditional vaccines (whole killed pathogens, live attenuated pathogens, subunits (antigens) derived from pathogens, or inactivated pathogenic toxins), plasma-derived products and cellular and tissue products for transplantation [3]. Such substances were always considered too complex and heterogenous to be defined sufficiently. An alternative WHO expert committee, the Expert Committee for Biological Standardisation (ECBS), was established in 1946 to work on standardisation of complex biological substances such as blood products and the antigenic substances that make up vaccines [6]. This work continues to this day and is a highly specialised, vital and important function for the control of these substances. The ECBS also introduced requirements for quality aspects since the control of these complex biological substances relies as much on their manufacture as on the characterisation of the final product. Nowadays many such WHO requirements have been drafted by the ECBS, both general requirements for their manufacture, control and standardisation, and requirements for specific substances, such as a specific blood coagulation factor or a specific vaccine antigen. Included in these requirements is a suggested global international name for such products; these are short descriptive names that are common to all vaccines of the type in question and so quite separate from the uniqueness imbued by an INN. Thus, given the complexity of traditional vaccines and the provision of these short descriptive names by the ECBS, the INN Programme has precluded the assignment of INN to vaccines such as live attenuated vaccines, inactivated pathogens and toxoids [3].

During the INN Consultation in 1993, however, and following on from naming recombinant DNA-derived therapeutic proteins, it was agreed that recombinant protein vaccines may fulfil the requirements of being defined and homogeneous substances [7] and so could be assigned INN, and this position remains [7] . Also, note that while natural plasma-derived products are not named, their recombinant well-defined counterparts such as recombinant coagulation factors are included in the nomenclature scheme. The INN Programme has also stated that chemically synthesised peptides used as vaccine antigens can be assigned INN as they are also well-defined [7]. Requesting an INN for a drug substance is not mandatory (unless specified by a regulatory authority, for instance) and to date no INN have been sought (or given) for any of the few recombinant protein vaccines on the market or under development. Several INN have been assigned to the active substances of therapeutic peptide vaccines although these so-called cancer vaccines are immunomodulatory in action rather than being prophylactic.

3. INN for vaccine active ingredients

Early vaccines were complex entities whose quality could only be assured by control of their production as well as their final characterisation. As mentioned above they were assigned a short descriptive name by the ECBS. Nowadays, vaccines have been and are being developed through numerous approaches. In 2015, an INN was requested and assigned for the first time to the active ingredient of a prophylactic vaccine against a microbial pathogen, in this case a rabies vaccine [8]. The active ingredient of this vaccine is a defined messenger RNA (mRNA) molecule that acts by expressing a rabies antigen in the vaccine recipient [8]. The mRNA was assigned the name *nadorameran*, a name in which the suffix -*meran* refers to the mRNA nature of the substance whilst the random *nadora*- prefix makes the name distinct and unique. With the COVID-19 pandemic, a myriad of vaccines against SARS-CoV-2 virus are being developed with some now being administered under emergency authorisation. A few of these applied for and were assigned INN at an *ad hoc* meeting of the INN Expert Committee in August 2020 (Table 1, [9]). Among these was one plasmid DNA vaccine and several mRNA vaccines, with both types lending themselves to be well-defined and eligible for assignment of INN. Meanwhile other INN applications for vaccine substances have followed [10].

As of November 2021, the list of 326 vaccines under investigation for combatting the COVID-19 pandemic illustrates the various modern approaches that are being followed in vaccine develop-

Table 1
INN assigned to active ingredients of prophylactic DNA and RNA COVID-19 vaccines[1].

INN	technology	encoded antigen structure	applicant
reluscovtogene ralaplasmid[2]	plasmid DNA	full-length SARS-CoV-2 spike glycoprotein	Inovio Pharmaceuticals
zorecimeran[3]	mRNA	full-length SARS-CoV-2 spike glycoprotein	CureVac
abdavomeran	mRNA	receptor binding domain of the SARS-Cov-2 spike glycoprotein fused with the T4 fibritin domain	BioNTech
tozinameran	mRNA	full-length SARS-CoV-2 spike glycoprotein	BioNTech
ganulameran	mRNA	receptor binding domain of the SARS-CoV-2 spike (S) glycoprotein connected to the T4 fibritin and the S glycoprotein transmembrane domain	BioNTech
pidacmeran	Self-replicating mRNA	full-length SARS-CoV-2 spike glycoprotein	BioNTech
elasomeran	mRNA	full-length SARS-CoV-2 spike glycoprotein	Moderna

[1] These INN were published in [9] and [10].
[2] the nomenclature scheme for plasmid DNA comprises two-words: the first word ends with the stem *-gene* and has an infix describing the nature of the transfected gene, in this case *-covto-* for SARS-Cov-2 gene; the second word pertains to the vector which in this case is a plasmid DNA [7].
[3] the nomenclature scheme for messenger RNA substances comprises one word ending in *-meran* preceded by a random fantasy prefix [7].

Table 2
Examples of INN assigned to therapeutic plasmid DNA, virus-vectored and virus active substances[1]

INN	vector	transgene	indication
quaratusugene ozeplasmid pL124[2]	plasmid DNA	tumour suppressor candidate 2 (TUSC2)	advanced non-small cell lung cancer
bizalimogene ralaplasmid pL118	plasmid DNA	E6 and E7 proteins of human papilloma virus 18	HPV-induced pre-malignancy
verbrinacogene setparvovec pL122	adeno-associated virus (parvovirus)	human coagulation factor IX (hFIX)	haemophilia B
patidistrogene bexoparvovec pL124	self-complementary adeno-associated virus (parvovirus)	human alpha-sarcoglycan (hSGCA)	limb girdle muscular dystrophy
encoberminogene rezmadenovec pL124	adenovirus	multiple human vascular endothelial growth factor (VEGF) isoforms (VEGF121, VEGF165 and VEGF189)	refractory angina
inetagugene geperpavec pL124	herpesvirus	human transglutaminase 1 (TGM1)	autosomal recessive congenital ichthyosis
suratadenoturev pL123	adenovirus	E1A and E1B genes controlled by human telomerase reverse transcriptase (hTERT)	antineoplastic

[1] the nomenclature scheme for plasmid DNA is mentioned in a footnote to Table 1. The nomenclature scheme for virus vectors similarly comprises two-words: the first word ends with the stem *-gene*, has an infix describing the nature of the transfected gene and begins with a random fantasy prefix. The second word pertains to the vector and specific stems have been assigned depending on the nature of the virus. Where a genetically engineered cell is the active substance, a similar scheme operates with the second word ending in -cel. The nomenclature scheme for virus-based therapies is one word ending in *-rev* with infixes such as *-tu-* for tumouricidal, an infix for the nature of the virus and a random prefix [7].
[2] Proposed Lists (pL) of INN are available on the WHO/INN website (Health product and policy standards (who.int)).

ment, including recombinant protein, DNA, RNA, peptide and vectored vaccines [11]; indeed, of the 132 vaccines that are already in clinical development for COVID-19, 113 are based upon these new innovative approaches with only 19 relying on the more traditional methods.

The following outlines the multitude of vaccine technologies and the extent to which each vaccine could be assigned INN.

4. Modern vaccine Developments

4.1. RNA

One of the most recent approaches to vaccine development involves messenger RNA (mRNA) [12]. The mRNA contains a gene encoding the relevant protein antigen which (unlike a DNA vaccine) is expressed directly in the cytoplasm of recipient's cells. Several mRNA anti-SARS-CoV-2 vaccines are under development and some have been authorised for use. The mRNA is usually well-defined, and some mRNAs have already been assigned INN including the aforementioned rabies mRNA vaccine and several for COVID-19 mRNA vaccines (Table 1). One drawback is that mRNA is labile, needs to be formulated in a manner to protect the RNA from degradation, and requires a delivery system to transport the RNA into the cell; current COVID-19 mRNA vaccines are formulated in lipid nanoparticles to address these challenges. An extension of this involves self-amplifying mRNA vaccines which, in addition to encoding the gene for the desired antigen, incorporate virus-derived genes that encode enzymes that replicate the RNA intracellularly, thus increasing the number of mRNA molecules that can be translated into antigen [13]. Note that the INN applies to the mRNA and not to the final formulated vaccine. In addition, the INN comprises the complete mRNA structure, and mRNAs with identical coding regions but distinct non-coding regions, would have separate INN.

4.2. DNA

DNA vaccines, primarily using bacterial cultured plasmid DNA, naked or complexed, have been under development for some time but with little success in the human field [14]. No DNA vaccine has yet been authorised for use in humans although a few have been authorised for veterinary use and several DNA-based anti-SARS-CoV-2 vaccines have entered phase III clinical trials. The vaccines function typically by expression in the recipient of a gene encoding a protein antigen of the pathogen concerned under control of mammalian promoters. Thus the drug substance of a DNA vaccine is equivalent to a plasmid DNA being used as a therapeutic agent in which a therapeutic protein is encoded rather than a protein antigen. DNA used as a vaccine or a therapeutic vector will be homogeneous and well-defined, thus making it suitable for the assignment of INN. Indeed, several DNA drug substances, for example the antineoplastic *quaratusugene ozeplasmid* (Table 2), the therapeutic DNA vaccine *bizalimogene ralaplasmid* expressing antigens of human papillomavirus for the treatment of HPV induced disease (Table 2), and the anti-SARS-CoV-2 DNA vaccine *reluscovtogene ralaplasmid* (Table 1), have already been assigned INN.

4.3. (Recombinant) protein subunits

Protein subunit vaccines manufactured by recombinant DNA technology comprise a specific protein antigen(s) of the pathogen and are not to be confused with the traditional manufacture of subunit vaccines by which a microorganism is subjected to chemical dissociation and the appropriate antigenic component is isolated [15]. Many vaccines but especially protein subunit vaccines contain an adjuvant to boost the immune response [16]. These are part of formulation and would not be taken into consideration in assigning an INN.

A wide variety of cell expression systems are available for the industrial manufacture of recombinant proteins and include bacteria, yeast, plant, insect and mammalian cell types. Recombinant proteins have been developed and manufactured for some time as therapeutically useful pharmaceutical substances and these have been assigned INN; indeed, such substances, e.g. monoclonal antibodies, epoetins, coagulation factors, form a major proportion of current requests for INN. A recombinant protein intended for active immunization can similarly be assigned an INN and in 1993 it was agreed that recombinant protein vaccines may fulfil the requirements of being well-defined and homogeneous substances [7] and so could be assigned INN.

In 1986, a yeast derived recombinant hepatitis B vaccine, containing the hepatitis B surface antigen was the first vaccine of any kind manufactured by recombinant technology [17]. Since then, recombinant protein subunit vaccines against influenza [18], human papilloma virus [19] and *type B meningococcal* (MenB) bacterium [20] have been authorised for use. The expressed proteins may exist as a soluble protein (recombinant influenza HA, influenza vaccine; recombinant MenB surface proteins (MenB vaccine), an outer membrane vesicle with a recombinant protein (MenB vaccine), a membrane associated particle (recombinant HBsAg, HBV vaccine) or self-assemble into a virus like particle (recombinant HPV E6/E7, HPV vaccine). However, to date, no INN has been requested for a recombinant protein for use as a prophylactic active immunisation agent against a microbial pathogen.

In contrast, in 2005, a recombinant fusion protein comprising the BCG heat-shock protein HSP 65 fused to transcription factor E7 of human papilloma virus (HPV) 16 for treatment of cervical cancer was assigned the INN *verpasep caltespen* [21].

4.4. Peptides

Considerable research has gone into the development of synthetic peptides as vaccines although none have yet been approved for prophylactic use against an infectious disease [22]. In an alternative area of research, synthetic peptides have been widely investigated for use in various diseases such as cancer, where an appropriate immune response against a tumour antigen is sought that will inhibit or at least modulate the growth or spread of a tumour [23]. In other instances, peptides (including chimeric peptides) are being investigated for treatment of diseases such as Alzheimer's and multiple sclerosis by either initiating or repressing the induction of an immunomodulatory response, respectively. These substances are chemically well-defined, and many of them have been assigned INN with the stem *-motide* for peptides used for active immunization (Table 3); however, none of these has reached marketing authorization. A fully prophylactic anti-pathogen synthetic peptide vaccine would similarly be well-defined and could be assigned an INN, including cocktails of peptides in which each peptide would be assigned an individual INN.

Table 3
Examples of the use of *-motide* as INN stem for peptides used for active immunization (cancer treatment).

INN	Structure/Description
baloramotide *pL120*	182 amino acid recombinant NY-ESO-1 protein glycyl-L-prolyl-human cancer/testis antigen 1 (autoimmunogenic cancer/testis antigen NY-ESO-1, L antigen family member 2 LAGE-2), cancer/testis antigen 6.1, CT6.1), produced by *Escherichia coli*
nelatimotide *pL115*	19 amino acid peptide L-cysteinyl[human Wilms tumour protein (WT33)-(126–134)-peptide] (1–10) and [236-L-tyrosine(M > Y)]human Wilms tumor protein (WT33)-(235–243)-peptide (1′-9′), (1–1′)-disulfide
tanurmotide *pL109*	10 amino acid peptide human lymphocyte antigen 6 K-(101–111)-peptide
zastumotide *pL110*	450 amino acid recombinant protein 19,137,308,342,395-penta[S-(2-amino-2-oxoethyl)]-{[2 aspartic acid(K2 > D),3-proline(L3 > P)]glycerophosphoryl diester phosphodiesterase (Haemophilus influenzae strain 86-028NP EC 3.1.4.46)-(1–127)-peptide fusion protein with [2-aspartic acid(P2 > D)]human melanoma-associated antigen 3 (MAGE-3 antigen, antigen MZ2-D, cancer/testis antigen 1.3 or CT1.3) fusion protein with diglycylheptahistidine}

4.5. Viral vectors

In 1996, the INN Programme decided that gene therapy vectors could be assigned INN as they are sufficiently defined to make them distinct and unique. These vectors comprise recombinant viruses and INN have been assigned to vectors based upon parvoviruses, lentiviruses, herpesviruses, adenoviruses and poxviruses (Table 2); INN have also been assigned to some bacterial vectors. Viral vectors for gene therapy are designed to express a therapeutic protein [24]. Viral vectors used as vaccines are designed to express a protein antigen to raise an immune response against a specific pathogen. Virus vectors can be replicating or non-replicating and both DNA and RNA viruses are being used. Several vaccines of this type have been approved for use in humans including vaccines against Ebola, Japanese encephalitis and COVID-19 (Table 4). Many viral vectored vaccines are also authorised for veterinary use.

Viral vectors, whether designed to express a therapeutic protein or to express a protein antigen for induction of an immune response (therapeutic or prophylactic vaccine), fulfil the requirements for assignment of an INN. Therapeutic viral vectors are

Table 4
Examples of virus vectored vaccines.

Disease target	Virus vector	Transgene	Name
Japanese encephalitis	Yellow fever live attenuated vaccine strain 17D	JE prM-E	Imojev (Sanofi Pasteur)
Ebola	vesicular stomatitis virus (VSV)	Ebola Virus Zaire (ZEBOV) surface glycoprotein	Ervebo (Merck)
Ebola	adenovirus 26	Ebola Virus Zaire (ZEBOV) surface glycoprotein	Zabdeno (Janssen)
COVID-19	chimpanzee adenovirus Y25	SARS-Cov-2 spike protein fused with tPA leader	ChAdOx1 nCov-19/Vaxzevria (AstraZeneca)
COVID-19	adenovirus 26 + adenovirus 5	full-length SARS-Cov-2 spike protein	Sputnik V (Gamaleya)
COVID-19	adenovirus 26	full-length SARS-Cov-2 spike protein	Janssen COVID-19 Vaccine (Johnson & Johnson)

now routinely assigned INN (Table 2); however, to date no INN has been published for a prophylactic viral vectored vaccine.

In addition to viral vectors, INN have also now been assigned to well-defined recombinant viruses being used therapeutically to treat tumours, and which are referred to as oncolytic viruses (see *suratadenoturev* Table 2).

5. Traditional vaccines

No INN have been assigned to the following types of traditional vaccines (see also [25]) which have been given short descriptive names by the ECBS.

5.1. Inactivated (whole/subunit) or killed

Inactivated vaccines contain whole microorganisms chemically inactivated in a way that is not detrimental to the desired immune response [25]. In some cases, the inactivated pathogen may be further treated to produce a subunit comprising the desired antigen. Although the nucleotide sequence of the master virus stock could be analysed, it may not be determined that it is a single species. In addition, the structure of the inactivated particle does not lend itself to precise characterisation, especially in subunit format. Consequently, it is unlikely that an inactivated vaccine is suitable for INN.

5.2. Live attenuated

Live attenuated viral vaccines are the most effective vaccines to date [26]; they comprise live pathogens that although infectious, no longer induce disease in the recipient. Common and successful live attenuated viral vaccines include those against polio, yellow fever, tuberculosis, measles, mumps, rubella, influenza, and others. The homogeneity of a master stock of vaccine virus may not have been determined and to date most (if not all) such vaccines have been given an international common name by the ECBS. In general, they may not be amenable to having an INN as they may not be a clonal, well defined species. However, if the attenuation was to be achieved by precise genetic engineering, they may be suitable for INN.

5.3. Conjugate vaccines

Several bacterial vaccines are conjugate vaccines [27]. The antigenic component of these is complex polysaccharide on the surface of the bacteria. In conjugate vaccines, the isolated bacterial cell surface polysaccharide is attached, or conjugated, to an entity such as diphtheria toxoid or tetanus toxoid protein that acts to enhance the immune response. These vaccines have complex polysaccharide structures and are likely not suitable for INN.

5.4. Toxoids

In some bacterial infections e.g., diphtheria and tetanus, the basis of the disease is a toxin produced by the bacterium. Chemically modified/inactivated toxins, called toxoids, can be used to generate an immune response which protects the recipient from disease (but not from infection) [25]. While detailed information on the structure of protein toxins is available, the nature of chemically inactivated toxin is much less precise and is not appropriate for an INN. However, a recombinant genetically inactivated toxin being developed as a vaccine could be amenable to assignment of an INN [28].

In summary, the vaccine types outlined under "Modern Vaccine Developments" can be assigned INN by the WHO INN Programme. To date only a few vaccines have been assigned INN including mRNA and DNA vaccines with others pending. The traditional vaccine types are not suitable for INN and general descriptive names are suggested by the WHO ECBS.

6. The value in assigning INN to vaccine active ingredients

The INN nomenclature system was developed to assign unique names to well-defined, distinct pharmaceutical substances to ensure their global recognition. INN have proven to be indispensable for the clear identification, safe prescribing and dispensing of medicines; they also enhance pharmacovigilance by facilitating communication and exchange of information among health professionals. This is achieved, as stated earlier, by assigning a distinct, unique name, placed in the public domain to each well-defined pharmaceutical substance. Although many prophylactic vaccines against infectious diseases are used in public health programmes and are not directly prescribed on an individual patient basis, they are administered to very large numbers of individuals, and especially in the current COVID-19 pandemic, there needs to be clear identification of the many individual SARS-CoV-2 vaccines in order to undertake proper pharmacovigilance to ensure the ongoing safety of vaccine recipients.

Furthermore, in view of the appearance of SARS-CoV-2 variants of concern (VOC), some vaccine developers are updating their vaccines in an accelerated manner to tackle these variant strains. Any changes to the vaccine ingredient sequence (nucleotide or amino acid) would require in principle a new INN. To this end, the INN Programme has issued notice that the INN for a vaccine active substance re-designed to combat SARS-CoV-2 variants of concern, will be linked to the original INN (where one exists), by the addition of a short, random, 2–3 letter syllable as a prefix to the original INN [29]. No other modification of a vaccine substance INN is envisaged or needed. Additionally, the INN assignment process will be accelerated so that the INN for the variant vaccine substance can be incorporated into packaging, package inserts and labels as soon as a variant vaccine is ready for use. Having linked INN for both original and variant COVID-19 vaccine substances will be of great benefit in their use and in pharmacovigilance. Clear identification is also crucial in immunisation regimens involving heterologous combinations of vaccines [30]. Such regimens are currently being tested by alternating virus-vectored vaccines with RNA vaccines in the UK [31] and elsewhere by testing dosing schedules that involves the sequential administration of two distinct virus-vectored vaccines [32].

Monitoring of adverse events following immunization (AEFI) is an essential practice in ensuring the safety of vaccines and is now an integral part of vaccine regulation, and surveillance systems exist at national and international levels to ensure effective monitoring and prompt action in response to AEFIs. Undoubtedly, INN would contribute immensely to identifying COVID-19 vaccines, especially altered versions and the use of combinations. However, it is recognised that for a full track and trace system, additional measures such as barcoding that captures batch number and expiry data, access to manufacturers' traceability data, and the mandatory recording of immunization acts, would be required [33]. Various projects are ongoing to digitise identifiers for substances and products and all refer to INN, including INN information. This enhances the importance of INN as the global harmonized name for substances, including vaccines [34].

An issue that may impede the assignment of INN to vaccine antigens is the valency of the final vaccine product as vaccines often contain several antigens corresponding to various strains of the targeted pathogen. For example, influenza vaccines typically contain 3 or 4 individual antigens representing different strains of the virus

against which immunity is sought [18]. For such a recombinant multi-antigenic influenza vaccine, it is anticipated that each antigen would require its own INN. Several recombinant human papilloma vaccines (HPV) are authorised for use and these also contain multiple individually expressed protein antigens; one such vaccine has two individual protein antigens, one has four individual protein antigens and one is nonavalent, containing nine individual recombinant protein components [35]. Three of the proteins in a type B meningococcal vaccine are made using recombinant technology [20]. In each of the above cases, INN would be assigned to each protein antigen and not to the final vaccine product.

Furthermore, specifically for influenza vaccines, because of antigenic drift there is typically a need to change at least one of the recommended strains for inclusion in vaccine on an annual basis. Regardless of strain changes, manufacture of recombinant influenza vaccine on an annual basis following announcement of the strains to be incorporated and distribution of new season's vaccine on a timely basis could be at odds with the timeframe for an INN to become recommended (around 16–18 months) thereby impacting the feasibility of including such INN on labels and other presentation materials for the vaccine. To overcome this, the WHO INN Programme is investigating the establishment of a special process for the rapid assignment and approval of INN for well-defined vaccines that require to be manufactured and deployed in a short time frame; indeed, such a procedure has been initiated with the development of an accelerated INN assignment process for variant COVID-19 vaccines [29]. Requests for INN for other COVID-19 related substances are also being assessed and published on a priority basis.

It should be highlighted that INN assignment is predicated upon the submission of a request from a sponsor/applicant and is not a WHO mandatory process, although certain regulatory settings encourage submission of an INN request or to use an INN where there is one. To date, many vaccine developers and manufacturers have failed to submit prospective requests for INN for eligible vaccines. This omission is probably based on historical practice, as traditional vaccines were never assigned INN, but is perhaps also a result of lack of knowledge of the value of the INN, lack of awareness that INN can indeed be assigned to certain vaccine ingredients, and the absence of any impetus from regulatory authorities to encourage sponsors to apply for INN. Consistent with common practice for chemical and biological therapeutic drug substances, developers of eligible vaccine products should apply for an INN as soon as clinical trials have been initiated as the value of the INN in safe prescribing and pharmacovigilance is well established.

INN nomenclature offers a well-established, clear and non-technology-based system for global recognition of eligible vaccines which benefits the vaccine recipient, health care professionals and pharmacovigilance experts by facilitating the tracking of recipient exposure to a particular vaccine. To safeguard vaccine recipients in the current environment of an armamentarium of multiple vaccines to prevent infection by SARS-CoV-2, the WHO INN Programme urges vaccine developers to request INN for well-defined vaccine ingredients and encourages regulatory authorities to facilitate INN implementation [5].

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Credit authorship contribution statement

James S. Robertson: Conceptualization, Writing – original draft, Writing – review & editing. **Ursula Loizides:** Writing – original draft, Writing – review & editing. **Akinola Adisa:** Writing – review & editing. **Ana López de la Rica Manjavacas:** Writing – review & editing. **Vicente Rodilla:** Writing – review & editing. **Colette Strnadova:** Writing – review & editing. **Karin Weisser:** Writing – review & editing. **Raffaella Balocco:** Conceptualization, Writing – review & editing.

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