Is suspension of Anti-Sars-Cov2 Vaccine Patents the most appropriate and feasible strategy to deal with the Covid-19 public health emergency ?

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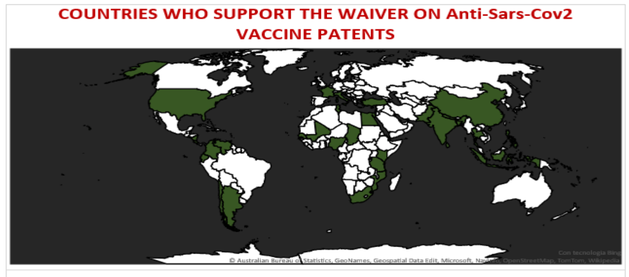
INTRODUCTION
Every generalized health emergency - whether the appearance of HIV or the Covid-19 pandemic - triggers acrimonious debate on the need to suspend patents covering agents necessary to fight the disease.

The aim of this work is to contribute positively to the discussion on the *suspension of patent rights* - relating to anti-SARS-CoV2 (COVID-19) vaccines - through rigorous and objective analysis of the various aspects involved.



On the 2th of October 2020, India, Sud Africa, Kenya and Eswatini proposed officially to the WTO a waiver on the Anti-Sars-Cov2 Vaccine patents. Many countries(in green) give their support to this request:
Argentina, Bangladesh, Egypt, Indonesia, Mali, Mauritius, Mozambique, Nepal, Nicaragua, Pakistan, Sri Lanka, Tunisia, Venezuela, Chad (least-developed countries (LDC) Group), Chile, China, Colombia, Costa Rica, Ecuador, El Salvador, Jamaica (African, Caribbean and Pacific countries (APC) Group), Nigeria, Philippines, Senegal, Tanzania (Africa Group), Thailand, Turkey, and recently United States, France and Italy.

The Waiver:
AN *EXCEPTION* TO A GENERAL RULE
(Art. IX § 3, 4) Marrakesh Agreement

Does the suspension of the patent rights, deriving from the granted patents, ALLOW THIRD PARTIES TO PRODUCE AND USE SUCH VACCINES FREELY ?

TO ANSWER, WE MUST:
1) trace the components of these vaccines in the technical documentation filed with the EMA (at the request of the Market Authorization - MA)

2) verify, through Freedom to Operate, if Pfizer, Moderna, Astrazeneca and Johnson & Johnson own all patent rights relating to these components, necessary for production, without incurring infringements

mRNA VACCINES

mRNA VACCINES COMPONENTS

1) The SPIKE protein as an immunogen is present both in the Biontech/Pfizer vaccine and in the Moderna vaccine. The SPIKE protein, in pre-fusion conformation, compared to the post-fusion one, increases the neutralizing and protective efficacy of the vaccine. However, the pre-fusion conformation is unstable → **the problem has been solved by producing a variant of the SPIKE protein, called SPIKE-2P.**

→ **The SPIKE-2P** protein is protected by the:
→ **US patent 10.960.070 (30/03/21)** and
→ **WO2021 /123365** the OWNERS of these patents are:
- **NIH**
- **Scripps Research Institute**
- **Trustees from Dartmouth College**

→This means that the anti-Sars-Cov2 mRNA vaccines produced and marketed by **Pfizer-Biontech and Moderna** are likely to **depend on patents owned** by the NIH, Scripps Research Institute and Trustees from Dartmouth College.Therefore Pfizer and Moderna have most likely applied for the license on these patents

This means that all the vaccines produced and placed on the market against COVID-19 are likely dependent on the patents of the *United States of America* NIH, Scripps (US) and Dartmouth (US) protecting the spike-2P protein

2) The mRNA presents many critical issues:
-High instability;
-High immunogenicity;
-Poor efficiency in the translation of mRNA into proteins;
-Difficulty of administration.
From the **public assessment of the EMA** and the technical documentation for obtaining the MA, it is clear how **Biontech/Pfizer** and **Moderna** have solved these critical issues.

BIONTECH/PFIZER VACCINE
COMIRNATY

It features a synthetic mRNA

▲whose uridine residues are replaced with **N1-Methyl pseudouridine;**
▲ **It has a 3 'POLYADENINE tail and cap at the 5' end.**

These two modification:
i Increase the in vivo stability of the mRNA (otherwise it would be degraded by the endogenous nucleases);
ii Reduce the immunogenicity of mRNA, as it stimulates the TLR receptors and dendride cells to a lesser extent and reduces the production of TNF-α;
iii Increase the effectiveness of the translation;
▲**Further reduction of immunogenicity,** thanks to the use of a purified mRNA, which therefore has low amounts of contaminants (double-stranded RNA and truncated RNA).

MODERNA VACCINE
SPIKEVAX

Contains mRNA-1273, which is a synthetic mRNA

▲ **whose uridine residues** are replaced with **N1-Metilpseudouridina;**

▲ **At the 5 'end it has a cap and a 3' POLYADENINE tail.** These two changes were introduced for the same reasons mentioned above for Biontech/Pfizer.

▲ **It also presents the region 5 'and 3' NOT TRANSLATED (UTR) and open reading frame (ORF) in 5 '.**

▲ **Further reduction of immunogenicity, thanks to the use of a purified mRNA**, which therefore has low quantity of contaminants (double-stranded RNA and truncated RNA, without cap or polyadenine tail).

3) LIPID NANOPARTICLES (LNP) as a VECTOR
From the public assessment of the EMA and the technical documentation for obtaining the MA, it appears that both Biontech/Pfizer and Moderna, **use lipid nanoparticles to encapsulate mRNA**, in order to protect and administer the latter to patients.

BIONTECH/PFIZER VACCINE

→ **It uses 4 lipids to make up the lipid nanoparticle of interest:**
I. ALC-325 → is a cationic lipid;
II. ALC-159 → is a conjugated lipid (pegylated in this case);
III. DSPC → is a phospholipid, ied distearoyl phosphatidyl choline;
IV. CHOLESTEROL → serves to constitute, together with DSPC, a mixture that can be considered as a non-cationic lipid.

MODERNA VACCINE

→ **It uses 4 lipids to make up the lipid nanoparticle of interest:**
I. M-102 → is a cationic lipid;
II. PEG2000 DMG
III. DSPC → is a phospholipid, ie distearoyl phosphatidyl choline;
IV. CHOLESTEROL → serves to constitute, together with DSPC, a mixture that can be considered as a non-cationic lipid.

THE PATENTS PROTECTING THE BIONTECH/PFIZER mRNA VACCINE *COMIRNATY* are:
WO2021/188969A2
WO2021/213924A1
WO2021/213945A1

THE PATENTS THAT PROTECTING THE MODERNA mRNA VACCINE *SPIKEVAX* are:
WO2021/154763A1
WO2021/159130A2
WO2021/222304A2
WO2021/231963A1

THE PATENTS PROTECTING OF THE ASTRAZENECA DNA VACCINE *VAXZEVRIA* are:
GB161097.0
US2019175716A1
EP347543
GB2549809B

THE PATENTS PROTECTING THE JOHNSON & JOHNSON DNA VACCINE *JCOVDEN* are:
US62/969.00;
US62/994.630

DNA VACCINES

DNA VACCINE COMPONENTS

Astrazeneca Vaccine *VAXZEVRIA*	Johnson & Johnson Vaccine *JCOVDEN*
1) Primate adenovirus vector (chimpanzee)	1) Human adenovirus vector (Ad26)
2) DNA encoding a Sars-Coronavirus antigen	2) DNA encoding Sars-Coronavirus antigen

FREEDOM TO OPERATE ANALYSIS (FTO) DNA VACCINES

→ **As regards Astrazeneca vaccine,** the US patent US10124048B2 **(granted on 13.11.2018 to ISIS INNOVATION LTD),** which claims the Adenovirus vector and the DNA encoding a pathogen or tumor antigen ISIS INNOVATION LTD, **then transferred its patent rights to University Oxford Innovation,** which has developed a further **27 patent applications on adenovirus vectors:**
probably Astrazeneca has applied for a license to University Oxford Innovation to take advantage of this invention.

→ **As regards the Johnson & Johnson vaccine**, there are **78 Janssen Vaccine & Prevention patents** relating to adenoviral vectors for therapeutic purposes **(5 concern Sars Coronavirus antigens).**

→ **CONCLUSION: The FTO analysis shows that the suspension of patent rights on DNA vaccines would not allow third parties to freely produce such vaccines, as there would be counterfeiting of patents relating to the technologies and components necessary for their production.**

CONCLUSIONS:

Each vaccine is protected by a network of patent rights

An hypothetical *WAIVER* of the patent rights to be effective shall involve all the patents of the network

THE WAIVER IS NOT A GOOD WAY TO SOLVE AN EMERGENCY!!

..... FORESEE TODAY TO OVERCOME THE EMERGENCIES OF TOMORROW

FREEDOM TO OPERATE ANALYSIS (FTO) mRNA VACCINES

✻**The mRNA used by Biontech/Pfizer**, shows many characteristics of the synthetic mRNA protected by ***THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA*** patents:
- EP2578685B1
- US8278036B2
- US8691966B2
- US8748089B2
- US8835108B2
- US9750824B2

All vaccines use the spike protein (either DNA or mRNA) as immunogen;
• Many vaccines make use of Lipid Nano Particles (LNP) as carrier;
• All DNA-vaccines make use of an adeno-virus vector (either human or primate) to carry the spike protein DNA

→ In addition, **purified mRNA** is also protected by US111060107B2 patent, again owned by the *UNIVERSITY OF PENNSYLVANIA.*

✻ **The mRNA used by Moderna** has many characteristics of the synthetic mRNA protected by *THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA* patents:
- US8748089B2
- EP278685B1
- US8278036B2
- US8691966B2
- US8835108B2
- US9750824B2
- US111060107B2 (patent protecting, as mentioned above, the purified mRNA).

The US application US 26731209P del 07.12.2009, of "The Trustees of The University of Pennsylvania", has generated a family of 27 granted patents

→ **In addition, the presence of the UTR region in 5 'and 3'**, to increase the stability, the efficiency of translation and reduce the immunogenicity of the mRNA, is protected by various patents, also owned by *THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA.* They are generated by the international application WO2011/07193:
- US9371544B2
- EP2510099B1
- EP3112467B1
- EP3287525B1
- US10006007B2
- US8808982B2

All describe methods for obtaining low-immunogenicity mRNA:
highly purified mRNA;
free of RNA-fragments;
free of double stranded RNA;
free of un-capped 5'RNA

→ **CONCLUSIONS:** The FTO analysis shows **that both Biontech/Pfizer and Moderna must request a license** from the holder of these patent rights, which is *THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA.* Therefore, the suspension of the patent rights on these vaccines would not allow third parties to produce them freely, because it would be *infringment* of the patents owned by *THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA.*

On Espacenet it is deduced that Biontech/Pfizer and Moderna have a solid patent portfolio that claims and protects the mRNA formulated in lipid nanoparticles.
→ **Will these two companies be able to produce their own vaccines without the need for additional LNP licenses ? ?**

→ ▲ **Biontech/Pfizer vaccine**:
✻ ALC-325 → is protected since 2015 by US patents US10166298B1, US11040112B2 and European patent EP3532103A → are all owned by **Acuitas Therapeutics**.
✻ ALC-159 is protected since 2015 by the US patents US9737619B2 (claim 1) and by the European patent EP3532103A(claim 6) → these are also owned by **Acuitas Therapeutics.**

▲ **Modern vaccine**:
SM-102 → protected by international application WO2021/030701, owned by **Acuitas Therapeutics**;
→ Furthermore, the formulation used to constitute the lipid nanoparticle, both in the case of Biontech/Pfizer and in the case of Moderna, **is protected by the US'069 patent of Arbutus/ Protiva**, precisely because the latter claims and protects the LNPs used as vectors of nucleic acids (in this case mRNA) and made up as follows:
I. A cationic lipid (ALC-325 for Biontech/Pfizer; SM-102 for Moderna)
II. A non-cationic lipid (mixture of DSPC and cholesterol)
III. A conjugated lipid (ALC-159 for Biontech/Pfizer; PEG 2000 DMG for Moderna).

→ **CONCLUSIONS**: Both Biontech/Pfizer and Moderna are likely to have requested, as evidenced **by the FTO analysis**, non-exclusive licenses from **Arbutus/Protiva and Acuitas Therapeutics**.
Also in this case we have confirmation that the mere suspension of the patent rights of Biontech/Pfizer and Moderna on their vaccines would not be effective, as it would not allow third parties to freely produce such vaccines without legal consequences.

Patent/Published Application	Applicant/Assignee	Filing Date	Status	Invention Type
US 10,576,146	BioNTech	March 15, 2018	Active	Lipids/NP + mRNA
US 10,485,884	BioNTech	March 5, 2013	Active	Lipids/NP + mRNA
US 9,950,065	BioNTech	September 26, 2013	Active	Lipids/NP + mRNA
US2020/0155671	BioNTech	January 22, 2020	Pending	Lipids/NP + mRNA
US2020/0197508	BioNTech	March 21, 2018	Pending	RNA immune response
US2019/0153428	BioNTech	August 24, 2016	Pending	RNA immunogenicity
US2019/0321458	BioNTech	July 14, 2017	Pending	PC: Lipids/NP + mRNA
US2018/0263907	BioNTech	March 30,2016	Pending	Lipids/NP + mRNA
US2017/0273907	BioNTech	September 17, 2015	Pending	Lipids/NP + mRNA
US2014/0030808	BioNTech	December 2, 2011	Pending	RNA expression
WO2016/156398	BioNTech	March 30,2016	Published	Lipids/NP + mRNA
WO2015/043613	BioNTech	September 26, 2013	Published	Lipids/NP + mRNA
WO2013/087083	BioNTech	December 15, 2011	Published	Lipids/NP + mRNA

Patent/Published Application	Applicant/Assignee	Filing Date	Status	Invention Type
US 10,703,789	Moderna	June 12, 2019	Active	PC: Lipids/NP + mRNA
US 10,702,600	Moderna	February 28, 2020	Active	Betacoronavirus mRNA Vaccine
US 10,577,403	Moderna	June 12, 2019	Active	PC: Lipids/NP + mRNA
US 10,442,756	Moderna	December 18, 2017	Active	Lipids/NP + mRNA
US 10,266,485	Moderna	June 11, 2018	Active	Lipids/NP + mRNA
US 10,064,959	Moderna	April 21, 2017	Active	mRNA synthesis
US 9,868,692	Moderna	March 31, 2017	Active	Lipids/NP + mRNA
US2020/0206362	Moderna	October 11, 2019	Pending	PC: Lipids/NP + mRNA
US2020/0164038	Moderna	July 29, 2019	Pending	PC: Lipids/NP + mRNA
US2019/0015501	Moderna	September 27, 2018	Pending	Nucleic acid vaccine
WO2016/118724	Moderna	January 21, 2016	Published	Lipids/NP + mRNA
WO2016/118725	Moderna	January 21, 2016	Published	Lipids/NP + mRNA

Bibliography/ Sitography
EMA/707383/2020 Corr.1; 19 February 2021, https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty;
EMA/15689/2021 Corr.1; 11 March 2021, https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax;
https://worldwide.espacenet.com/
WO2021/188969-A2; WO2021/213924-Al; WO2021/213945-A1; WO2021/214204-A1; WO 2021154763 A1; WO 2021159040 A2; WO 2021159130 A2; WO 2021222304 A2: WO 2021231963 A1; US Patent 10,960,070; US16/344,774; US2021/0275664; WO2021/163365; WO2007/024708; EP2578685 B1; US8278036 B2; US8691966 B2; US8748089 B2; US8835108 B2; US9750824 B2; WO2011/071931; WO2014/160243;US11060107B2; US 9,404,127 US9,364,435; US8,058,069; US10166298-B1; US11040112-B2; EP3532103-A; US9737619-B2 (claim 1); EP3532103 (claim 6); WO2021030701; US9,404,127; US9,364,435; US8,058,069..

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51. IS SUSPENSION OF ANTI-SARS-COV2 VACCINE PATENTS THE MOST APPROPRIATE AND FEASIBLE STRATEGY TO DEAL WITH THE COVID-19 PUBLIC HEALTH EMERGENCY?

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During the Covid-19 pandemic, the exhaustingly heated debate on the advisability of suspending vaccine patents became a familiar topic not only among patent specialists but also to the general public. There were staunch defenders of patent protection and those for whom patents merely safeguard the economic interests of pharmaceutical companies and deny citizens' right to healthcare. Every generalized health emergency - whether the appearance of HIV or the current Covid-19 pandemic - triggers acrimonious debate on the need to suspend patents covering medical devices and agent necessary to fight the disease. The consensus view is that patent monopolies bar general access to therapeutic treatments. The frequently abstract, ideological and emotional tones adopted during the debate do not help objective assessment of the pros and cons of patent suspension and its feasibility.
This work aims to provide a clear, objective overview of what suspension of anti-SARS-CoV2 (COVID-19) vaccine patents would entail.
Three essential questions are considered:
First, what is the intended purpose underpinning any suspension of anti-Covid vaccine patents;
Second, what patents should be "suspended";
Third, what, if any, legal instruments exist that would enable rapid, effective patent suspension.

EMA/707383/2020 Corr.1; 19 February 2021,
https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty;
EMA/15689/2021 Corr.1; 11 March 2021,
https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax;
https://worldwide.espacenet.com/
WO2021/188969-A2; WO2021/213924-AI; WO2021/213945-A1; WO2021/214204-A1; WO 2021154763 A1; WO 2021159040 A2; WO 2021159130 A2; WO 2021222304 A2: WO 2021231963 A1; US Patent 10,960,070; US16/344,774; US2021/0275664; WO2021/163365; WO2007/024708; EP2578685 B1; US8278036 B2; US8691966 B2; US8748089 B2; US8835108 B2; US9750824 B2; WO2011/071931; WO2014/160243;US11060107B2; US 9,404,127 US9,364,435; US8,058,069; US10166298-B1; US11040112-B2; EP3532103-A; US9737619-B2 (claim 1); EP3532103 (claim 6); WO2021030701; US9,404,127; US9,364,435; US8,058,069.