


Patents and IP in the Age of COVID

U.S. Patent and Trademark Office

Biotech/Chemical Partnership Meeting

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Outline of the talk

- Basics of virology and vaccines
- COVID

- Vaccines generally
- COVID vaccines in development
- Patent matters
- Patent Licensing (compulsory and otherwise)

- Vaccine availability and accessibility
- Politics
- Future prospects
- Questions?

What is a virus?

- Obligate intracellular parasite, only replicates by using cellular machinery

- Comprised of either a RNA or DNA genome, that encodes protective coat of proteins
- The coat can comprise just proteins or viral proteins can be inserted into the cell membrane

- In that case the virus coat comprises viral proteins, cellular membrane and proteins, and polysaccharides

- Any of these components can be antigenic and hence can provide a source of vaccines

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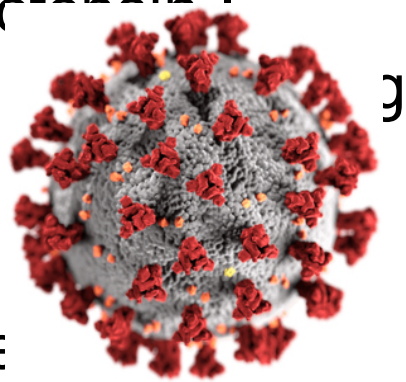
Coronaviruses

- Family of related viruses related to virus that causes the common cold and Middle East Respiratory syndrome

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause of the pandemic (COVID-19)
- Zoonotic viruses, infecting several vertebrate species

- Viral SPIKE protein binds to angi[illegible] converting enzyme 2 (ACE2) exp[illegible]g and other tissues

- Arose in bats (most likely)
- Novel human virus, recent transfe



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SARS-CoV-2 SPIKE protein

- Sequenced:

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSSTRGVYYPDKVFRSSVLHLTQDLFLPFFSN
VTWFHAIHVSGTNGIKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNA
TNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGK
QGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPPGFSALEPLVDLPIGINITRFQTLLALH
RSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS
FTVEKGIYQTSNFRVQPTDSIVRFPNITNLCPFGEVFNATTFASVYAWNRKRISNCVADYS
VLYNSTSFSTFKC
YGVSPTKLNDLCFTNVYADSFVITGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSK
HIDAKEGGNFNYLYRLFRKANLKPFERDISTEIYQAGSKPCNGQTGLNCYYPLYRYGFYP
TDGVGHQPYRVVVLSFELLNAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKK
FLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNASNQVAVLYQDVNCTE
VPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTN
SRSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDS
TECSNLLLQYGS
FCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIED
LLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTIT
SGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTAS
ALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSL
QTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFL
HVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVS
GSCDVVIGI
VNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNL
NESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAII
MVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

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Types of vaccines

- Whole live virus
  - Vaccinia virus (smallpox)

- Live Attenuated viruses, produced under selection for mutants with reduced virulence
  - Tuberculosis
  - Measles, mumps, rubella
  - Rotavirus
  - Chickenpox
  - Yellow fever

- Inactivated viruses (heat, chemical, genetic)
  - Rabies
  - Polio
  - Hepatitis A

Types of vaccines

- Subunit vaccines (coat proteins, envelope proteins)

  - Haemophilus influenzae type b
  - Hepatitis B surface antigen
  - HPV
  - Whooping cough
  - Pneumococcal

  - Meningococcal
  - Shingles
- Virus-like particles

- Nucleic acids (viral RNA and DNA (experimental))
  - Typically conjugated with lipid nanoparticles
  - E.g., 50:10:38.5:1.5 (ionizable lipid:DSPC:cholesterol:PEG-lipid)

Extant Viral Vaccines

TABLE 1. *Viral vaccines licensed in the United States*[a]

Virus vaccine	Number of serotypes covered by vaccine	Type of vaccine: Live	Type of vaccine: Nonliving	Target population	Comments
Adenovirus	2 (types 4 and 7)	+		Military recruits	Wild-type virus in enteric coated capsules for oral administration to selectively infect the gut; lapse in manufacturing
Hepatitis A	1		+	Travelers, health care workers	Parenteral immunization with whole inactivated virus vaccine, 2 doses
Hepatitis B	1		+	Universal childhood	Parenteral immunization with recombinant VLP, 3 doses
Influenza A and B	3 (H1N1, H3N2, and type B)		+	Elderly, patients with cardiopulmonary disease, others	Repeat annual parenteral immunization with disrupted virus vaccine
Japanese encephalitis virus	1		+	Travelers to endemic region	Parenteral immunization with whole inactivated virus vaccine
Measles	1	+		Universal childhood	Parenteral immunization; booster dose recommended at 4–6 years of age
Mumps	1	+		Universal childhood	Parenteral immunization; booster dose recommended at 4–6 years of age
Poliovirus	3	+	+	Universal childhood	Parenteral immunization with nonliving vaccine only is now recommended.
Rabies	1		+	High-risk persons	Prophylactic and therapeutic uses
Rotavirus	4	+		Universal childhood	Oral vaccine, three doses
Rubella	1	+		Universal childhood	Parenteral immunization
Smallpox	1	+		No longer used	Intradermal vaccine used to eradicate smallpox
Varicella	1	+		Universal childhood	Parenteral immunization
Yellow Fever	1	+		Travelers to endemic region	Parenteral immunization
Total number of viruses covered	22	16	10		

[a]See individual chapters for specifics on target populations and on schedules for immunization for individual agents, which can be more varied than presented in this overview. Rotavirus vaccine has been withdrawn from the market because of a concern over its possible association with intussusception.

VLP, virus-like particle

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COVID vaccines

- As of August 13th, according to the World Health Organization (WHO), there are 29 candidate vaccines undergoing clinical evaluation, and another 138 candidates in preclinical studies.
- Those in Phase III studies include:
  - two based on inactivated viruses, from the People's Republic of China (Sinovac and Sinopharm, the latter being developed by the Wuhan Institute of Biological Products and the Beijing Institute of Biological Products);
  - two RNA-based candidate vaccines: the Moderna/NIAID vaccine and the BioNTech/Fosun Pharma/Pfizer vaccine, both of which are lipid nanoparticle encapsulated RNAs;
  - The candidate furthest along (by accounts in the press) is the University of Oxford/AstraZeneca vaccine, based on a non-replicating viral vector.

COVID vaccines

- Those in Phase II studies include:
  - a non-replicating viral vector (Adenovirus Type 5) from the CanSino Biological Inc./Beijing Institute of Biotechnology;
  - a protein subunit vaccine from Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences

- Those in Phase I/II include:
  - DNA-based vaccines (from Inovio Pharmaceuticals/ International Vaccine Institute, Osaka University/ AnGes/ Takara Bio, Cadila Healthcare Limited, and Genexine Consortium);
  - protein subunit vaccines (from Kentucky Bioprocessing, Inc. and Novavax), RNA (Arcturus/Duke-NUS); and
  - non-replicating viral vectors (Janssen Pharmaceutical Companies), as well as a vaccine based on whole virion inactivation (Bharat Biotech).

COVID vaccines

- Those in Phase I studies include:
  - a vaccine based on a measles-based replicating viral vector (Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme);
  - a plant-derived virus-like particle (VLP)-based vaccine (Medicago Inc.) and
  - non-replicating viral vectors (from Gamaleya Research Institute and ReiThera/LEUKOCARE/Univercells);
  - subunit vaccines, including a "native-like trimeric subunit Spike protein vaccine" (Clover Biopharmaceuticals Inc./GSK/Dynavax is developing) and a vaccine based on a recombinant Spike protein formulated with Admax™ adjuvant (Vaxine Pty Ltd/Medytox); and
  - RNA-based vaccines (Cirevac and Imperial College of London

Vaccines in Phase III

Developer	Type	Component	Dose
University of Oxford/Astra Zeneca	Non-replicating viral vector	ChAdOx1-S	One IM dose
Sinovac	Inactivated	SARS-Cov-2	Two IM doses/14d
Wuhan Institute of Biological Products/Sinopharm	Inactivated	SARS-Cov-2	Two IM doses/14-21d
Beijing Institute of Biological Products/Sinopharm	Inactivated	SARS-Cov-2	Two IM doses/14-21d
Moderna/NIAID	RNA	LNP-RNA	Two IM doses/21d
BioNTech/Fosun Pharma/Pfizer	mRNA	LNP-RNA	Two IM doses/28d

Vaccines in Phase II

Developer	Type	Component	Dose
Cansino Biological Inc/Beijing Institute of Biotechnology	Non-replicating viral vector	Adenovirus Type 5 vector	One IM dose
Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Protein subunit	Adjuvanted recombinant protein	Two or three IM doses/ 28d

Vaccines in Phase I/II

Developer	Type	Component	Dose
Chinese Academy of Medical Sciences	Inactivated	SARS-Cov-2	Two IM doses/28d
Inovio Pharmaceuticals/IVI	DNA	DNA plasmid vaccine with adjuvant	Two IM doses/28d
Osaka University/ AnGes/ Takara	DNA	DNA plasmid with adjuvant	Two IM doses/14d
Cadila Healthcare Ltd	DNA	DNA plasmid with adjuvant	Three IM doses/28d
Genexine Consortium	DNA	DNA vaccine GX-19	Three IM doses/28d
Bharat Biotech	Inactivated	Whole SARS-Cov-2	Two IM doses/14d
Janssen Pharmaceutical	Non-replicating viral vector	Ad26COVS1	Two IM doses/56d
Novavax	Protein subunit	Recombinant SARS CoV- 2 glycoprotein nanoparticle	Two IM doses/21d
Kentucky Bioprocessing	Protein subunit	Spike protein RBD	Two IM doses/21d

Vaccines in Phase I

Developer	Type	Component	Dose
Arcturus/Duke-NUS	RNA	mRNA	IM dose
Gamaleya Research Institute	Non-replicating viral vector	Adenovirus	IM dose
ReiThera/LEUKOCARE/Univercells	Non-replicating viral vector	Adenovirus	IM dose
Clover Biopharmaceuticals /GSK/Dynavax	Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Two IM doses/21d
Vaxine Pty/Medytox	Protein Subunit	Recombinant spike protein	One IM dose
Univ. Queensland/ CSL/Seqirus	Protein subunit	Stabilized Spike protein	Two IM doses/28d

Vaccines in Phase I

Developer	Type	Component	Dose
Institute Pasteur/ Themis/Univ. of Pittsburgh CVR/ Merck Sharp & Dohme	Replicating viral vector	Measles based vector	One or two IM doses/28d
Imperial College London	RNA	LNP-nCoVsaRNA	IM dose
Curevac	RNA	mRNA	Two IM doses/28d
People's Liberation Army Academy of Military Sciences/ Walvax Biotech	RNA	mRNA	Two IM doses/14-28d
Medicago Inc.	Virus-like particle	Plant-derived, adjuvanted	Two IM doses/14-21d
Medigen Vaccine Biologics/NIAID/ Dynavax	Protein subunit	5-2P protein + CpG 10189	Two IM doses/21d

Pre-clinical vaccine candidates

- Of the 138 candidate vaccines in preclinical trials:
  - 12 are DNA-based;
  - 9 are inactivated virus;
  - 3 comprise live, attenuated virus;
  - 19 are non-replicating viral vectors, typically Adenovirus 5 or another adenovirus type;
  - 50 comprise protein subunits, often the viral Spike protein;
  - 17 are replicating viral vectors, using vesicular stomatitis virus, influenza virus, or other viruses;
  - 16 are RNA vaccines, usually mRNA-based; and
  - 12 comprise virus-like particles.

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Patenting

- Generally patents available for vaccines
- Patentable components include
  - Virus-derived protein or peptide antigens
  - Delivery agents, including nanoparticles
  - Formulations
  - Adjuvants

- Typically not a ”natural product” because changed from native state
  - Inactivated virus (treated with heat or chemicals)
  - Protein subunits, also including fragments formulated with non-naturally occurring substances
  - Nucleic acid viruses linked to lipid or other nanoparticles

Patenting

- No publicly available patents in U.S. on COVID 19 (not 18 months post-zoonotic transfer

- USP 10,130,701 patent to Pirbright Institute, with claims to live, attenuated coronavirus comprising a mutant replicase gene; this is a bird virus, NOT COVID

- China recently granted COVID 19 vaccine patent to CanSino Biologics for Ad5-nCoV vaccine
- Many previously conferred patents on vaccine components likely to be adapted to COVID 19 and provide ancillary (i.e., non-specific) patent protection to COVID 19 vaccine embodiments

- But likely that patents have been filed and will continue to be filed

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PTO Guidance

- Example 28 directed to pigeon flu virus vaccines
- Several varieties:

  - Live attenuated virus, bearing non-naturally occurring polymerase gene mutation
  - Inactivated (formalin treatment) virus
  - “Peptide F” vaccines, wherein peptide F is a naturally occurring peptide and claimed alone or with a pharmaceutically acceptable carrier which could be water; separately claim in more complex formulations

  - Peptide F mixed with conventional aluminum adjuvants

- All patent eligible except vaccines comprising Peptide F alone or in combination with carriers that include water
- Also eligible using vaccine delivery device

PTO Response to Pandemic

- USPTO took several steps to expedite patent prosecution regarding COVID

- In mid-March, the Office issued an announcement that the pandemic qualified as an “extraordinary situation” under PTO Rules 37 CFR 1.183 and 37 CFR 2.146, and petition fees waived for abandonment, but must attest that cause was COVID

- Coronavirus Aid, Relief, and Economic Security (CARES) extending deadlines for submissions that would create an obligation to pay certain fees, pursuant to the President’s declaration of a national emergency

PTO Response to Pandemic

- Applied to proceedings before the PTAB as well as before the Examination Division

- Also suspended requirement for original signatures in certain correspondence
- These provisions extended several times, now until September 30th

- Prioritized Examination Pilot Program permits an applicant who qualified for small (or micro) entity status to apply for existing “fast track” examination programs (which reach a patentability determination within 6 months) without paying the increased fees usually required for such filings for COVID-related applications

Compulsory licensing

- COVID pandemic has increased tensions between patent holders, governments, and international organizations

- Doha Declaration provides ability for governments to impose compulsory licenses within the GATT/TRIPS and WTO frameworks for diseases like COVID 19
- Some countries, including Canada, Germany, Israel, Chile, and Ecuador have already passed compulsory licensing legislation or resolutions backing compulsory licensing with respect to any COVID-19 vaccines and therapeutics.

- Alternative: voluntary patent pooling, e.g., under UN-backed Medicines Patent Pool (MPP), which was established in 2010 to expand access to tuberculosis, HIV, and hepatitis therapeutics

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U.S. Licensing

- "March in" rights under Bayh-Dole Act enable U.S. government to grant licenses based on Federally funded research
- 35 U.S. Code § 203: can require the grantee "to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances" or grant such a license itself
- Never been done and not available for products of privately funded research
- But recent history of industry out-sourcing to universities increases prospects

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U.S. Licensing

- Also reporting requirements can put patent rights at risk, requires notice of Federal funding on all patents
- Moderna challenged with non-compliance with Bayh-Dole reporting requirements
- 28 U.S. Code § 1498: statute developed for Second World War permits the government to grant non-exclusive licenses to industry for any patent obtained as a result of Federal funding
- Compensation to patentee limited to filing in the Federal Court of Claims
- Limited to “reasonable and entire compensation for such use and manufacture”

Availability and Accessibility

- Practical question: how to produce enough doses in a short enough time to be effective in stemming the pandemic and delivering these doses where they are most needed
- Some countries (including the U.S., 800 million doses + option on additional 1 billion doses, and UK, 340 million doses) have arranged contracts for vaccines from multiple sources
- Opposed by several international organizations, including WHO, the Coalition for Epidemic Preparedness Innovations, and the Global Alliance for Vaccines and Immunization

Availability and Accessibility

- Not unique: similar “vaccine hoarding” with the H1N1 influenza vaccine in 2009

- COVAX group attempting to have 2 billion doses in stockpile, with half directed to 92 low- and middle-income countries and the rest to 75 wealthier countries; 300 million doses (or promises) so far

- Challenge: even at $9/dose, that’s $18 billion
- "Patents and intellectual property are not what's standing in the way of fair distribution of COVID-19 vaccines; rather, equitable access and affordable prices require collaboration between governments and vaccine makers.” - Mark Feinberg, head of the International AIDS Vaccine Initiative in New York City

Availability and Accessibility

- Various estimates regarding how many doses *might* be available by year end 2021; 2-4 billion a reasonable guess
- Number needed depends on number of doses to achieve immunization (which varies from 1-3 in vaccines currently under development)

- And there remains the vagaries of distribution logistics, industrial-scale manufacturing, and perhaps most importantly the international politics.
- Consensus will be challenging

Politics

- US (and UK) refuse to join WHO declaration that COVID vaccines and medicines should be made available globally as “a public good”

- Will not join global patent pool
- May not matter, in view of WTO and Doha declaration

- USTR Special 301 Report as a way to deter international sanctions and compulsory licensing
- Nature of pandemic may reduce effectiveness of unilateral U.S. actions to protect patents

- In U.S., state attorneys general requesting Federal government to intervene to reduce cost and assure availability and accessibility

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Prospects

- Incredible uncertainty due to complexities of pandemic
- Challenges outside patenting issues
- But cannot ignore risk to global patenting if reason does not prevail
- Great incentives to forget the lessons of history regarding government control of drug (and vaccine) development
- But also not-so-recent examples (WWII) of government projects (antibiotic development, atomic weapons)
- Happy medium would be beneficial albeit unlikely

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Questions?

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Thank you!

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