Journal of COMMERCIAL BIOTECHNOLOGY

VOLUME 25 I NUMBER 3

ISSN: 1462-8732 / eISSN 1478-565X
WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

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Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 25 NUMBER 3 OCTOBER 2020

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Article

A Critical Review On Nano-Food Packaging and Its Applications

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ABSTRACT

The present manuscript addresses the effect of nanotechnology in various food sectors. Increased food functionality, enhanced flavor, reduced delivery of food additives are some of the appealing choices raising plausibility of high health advantages hypothesized in future. At the face of explosion of information, it is important to monitor them in a brief and updated manner. In this manner, new nanomaterials like carbon nanotubes, nano-biopolymers have diverse applications in food packaging, good food release property with enhanced food safety features. Furthermore, nano-encapsulation of probiotics, nano applications in food processing sector and other related issues, new functional nanomaterials for use in food along with their properties have been talked about in this review paper.

Journal of Commercial Biotechnology (2020) 25(3), 3–17. doi: 10.5912/jcb882
Keywords: nanopackaging, smart packaging,food additives, fortification.food processing, nanomaterial, nano foods

1. INTRODUCTION

Packaging of perishable food items is nowadays has been considered safe via nano packaging and has wider benefits in recent past (Garber, 2006). Therefore, food packaging can be classified into two broad categories (1) Food additives (aka= Nano inside) or (2) Food packaging (aka= Nano outside). Nano-outside has been more prevalent among customers because of high safety as compared to nano-inside packaging. (Garber 2006; Duncan 2011). (Ahmad et al., 2017).

Consumer's demand for both freshness and high nutrition has met with nano-packaged foods. Nano-packaged food items helps in the value addition of most of the food where they are considered as safe (Giles, Kuznesof, Clark, Hubbard, & Frewer, 2015). In this regard, nano-biocomposites are being developed to enhance the food stability by creating a barrier against gases to check it from food spoilage (Bajpai et al., 2018). Another successful noted example is the application of silver nanoparticles, for enhanced food safety and food preservation owing to its property as antibacterial agent, essential component in increasing the shelf-life of the food during preservation.Therefore, in this review we will discuss some important nano materials and their applications in food sector.

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2. NANOTECHNOLOGY MARKET IN FOOD SECTOR

Nanotechnology is emerging as a huge market because of its application in food processing sector and is expected to grow up to US$ 1 million by 2020 (Malanowski et al. 2008) with sale of nano-packaging products in 2004 with annual growth rate of 12-22% (Fletcher and Bartholomaeus 2011). This is witnessed by heavy investment in food nanotechnology research especially in food processing sector by global leaders *viz.* Nestle, H.J. Heinz, Unilever, Hershey and Kraft. USA, followed by Japan and China and around 500 other companies worldwide are investing in R&D, including some major international food and beverage companies. (Consultancy 2004). In 2008, packaging market was around 4.13 billion US dollars (globally) with an annual growth rate of 11.65%.

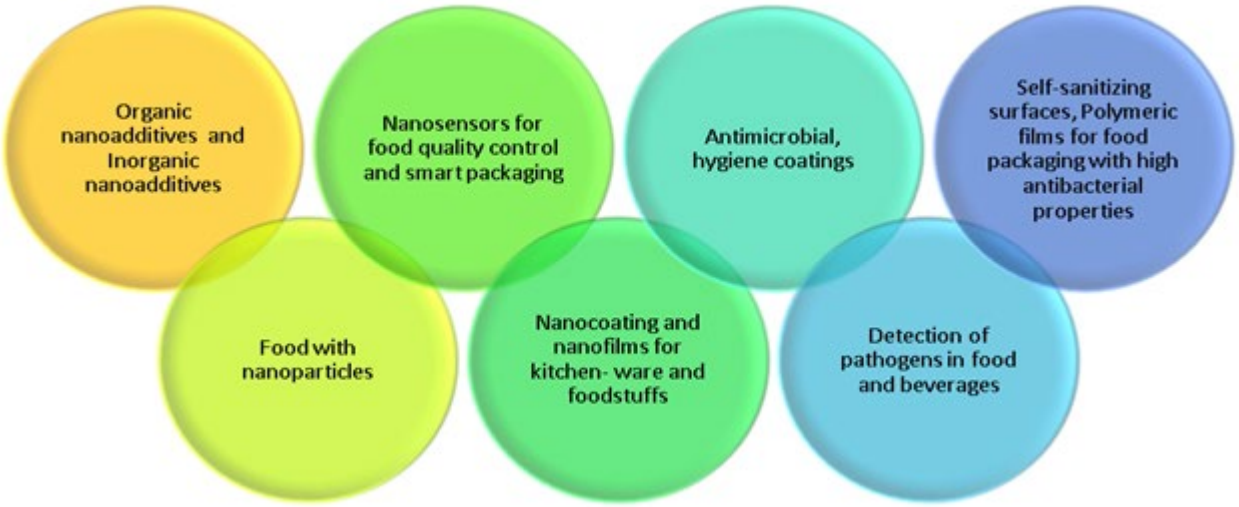

Figure 1: Applications of nanoparticles for variety of use in different food and agriculture sector.

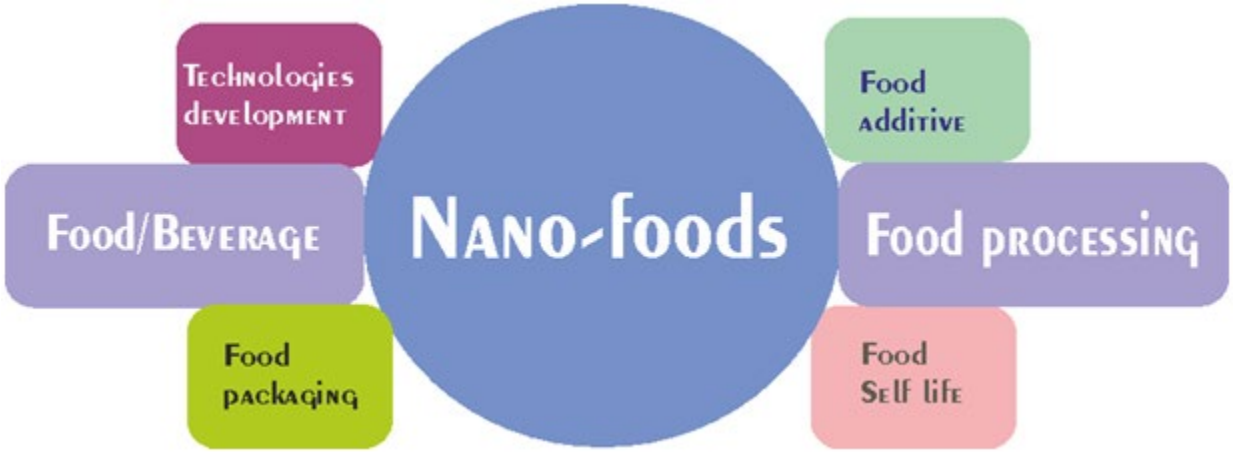

Figure 2: Nano food sectors can be divided into packaging, food shelf life, food additives and food beverages.

Thus nanotechnology is having a positive impact in food industry.Therefore, job market is also increasing reflected by a report where around 4 lakh job were provided in 2008 (including both public and private) and by 2020, at least 6 million jobs may be generated (Roco 2011). However public perception is always for "fresh" food as compared to nano-foods (Cobb 2005, 2011; Milan et al. 2013). The potential for nanoparticles in subsectors of the food sectors has been tabulated in Table 1.

3. NANOMATERIALS AND THEIR CLASSIFICATION

Nanomaterials should have specialized property if it has to be used in food sector viz. they must be economical and without any toxicity for use in perishable food items e.g. colloidal materials have sustainable quality, with enhanced efficiency suitable for food safety (Gokhale and Lee 2014).Nanotechnology is also extending its application in safe delivery of pesticides and fertilizers, in improving the textural property of food, in pathogen detection at an early stage of infections by using smart packaging system embedded with nano sensor.(Chau et al. 2007a). In this regard, nano-encapsulation and nano-emulsion has improved and revolutionized the (1) *agriculture* (pesticide delivery, pathogen detection) (2) *food processing* (for changing organoleptic properties) (3) *smart packaging* (via use of nano carriers, smart labels) (4) *food safety* (via use of nano silver as an antimicrobial agents) (Duncan 2011).Nano materials (NM's) are vital in food industry subsequently numerous nano structures are created like 1. Nano-particles (NPs), 2. Nano clays

Table 1: Overview of potential for nanoparticles in subsectors of the food sectors.

Food sectors-Processing value chain	Application	Types of Nanoparticles	References
1. Quality control	1. for chemical contaminants detection a. Uni-molecular sensors b. Sensor arrays c. Solid-state sensors 2. Sensors for detection of biological contaminants a. Electronic biosensors b. Optical Biosensors c. Mass-change biosensors	CNTs, NPs, Metal oxide nanoparticles Carbon nanotubes, nanoparticles Gold nanoparticles Tin, Indium, Zn oxides NPs Nanowires, CNTs, QDs, NPs Nanowires, carbon nanotubes, QDs, Au NPs, Pt-NPs, Biomems CNTs, Silica, Gold nanoparticles Au-NPs	(Chau et al. 2007b) (Robinson and Morrison 2010) (Baeumner 2004) (Viswanathan et al. 2006) (Bhattacharya et al. 2007) (Heugens et al.2010) (Yonzon et al. 2004)
2. Processing technology	1. Equipment's coating for disinfection 2. Filtration	Nickel, Ag, Carbon nanoparticles Nanoclays, TiO_2	(Basavaraja et al. 2008) (Chen et al. 2008a) (Chau et al. 2007c)
3. Functional foods	1. Delivery systems for nutrients 2. Edible coating	Natural food ingredients in the form of nanofibers or Nano films	(Bouwmeester et al. 2009) (Avella et al. 2005)
4. Packaging	1. Barrier packaging 2. Antimicrobial packaging 3. Biodegradable packaging 4. control of internal packaging environment 5. composites with Self-healing properties 6. Sensor technologies in packaging	Nano clays, TiO_2, acrylic NPs Ag, Zn incorporated in polymers Nanoclays, metal oxides in natural polymers, CNTs Nano porous calcium silicate, nanocrystalline titanium particles in an ethyl cellulose polymer film CdSe/ZnS NPs Fullerenes, TiO_2, nanoporous silica	(Robinson and Morrison 2010) (Berger 2008) (Sherman 2004) (Joshi et al. 2005) (Berger 2008) (Johnston et al. 2008) (Chau et al. 2007c) (Chen et al. 2008b)
5. Nutraceuticals delivery	1. Delivery of nutrients and functional ingredients 2. Release of nutraceutical compounds	Nanocapsules, liposomal nanovesicles, nanoparticles Nanospheres, Nano capsules	(ElAmin 2006) (Chen et al. 2006)

[a] *NPs; Nanoparticles, CNTs: Carbon Nano Tubes, QDs: Quantum Dots*

(NC's) and 3. Nano emulsions (NE's). Carbon nanotubes, inorganic nanotubes, nanowires, nano composite structures or nanoparticles of a specific substance, biopolymers, fullerenes, dendrimers and other nano materials developed for various applications. For nutraceuticals and probiotics delivery nano designing or quantum dots are developed as packaging materials, for improved effect(Kumari and Yadav 2014).

The nanomaterials are classified as follows:

i) Clay nanoparticles

Clay nanoparticles are the nanocomposites developed for enhanced food packaging by blending different polymers nanocomposites, for example, PA (polyamides), nylons, polyolefin, polystyrene (PS), ethylene-vinyl acetic acid derivation (EVA) copolymer, epoxy resins, polyurethane, polyimides and polyethylene terephthalate (PET).

Table 2: Different Nano techniques to encapsulate and delivery of functional ingredients.

Nanotechniques	Characteristic features	Examples	References
Edible coatings	For long storage it preserves the quality of the fresh foods	Gelatin-based edible coatings containing cellulose nanocrystal Chitosan/nanosilica coatings Chitosan film with nano-SiO2 Alginate/lysozyme nanolaminate coatings	Fakhouri et al., 2014 Shi et al., 2013 Yu et al., 2012 Medeiros et al., 2014
Hydrogels	Protection of drugs from harsh environmental conditions, delivery of the drugs placed in capsules to the desired target in response to external stimuli such as pH and temp.	Protein hydrogels	Qui and Park, 2001
Polymeric micelles	Improve the property of water insoluble compounds in hydrophobic interior environment.	PEO-b-PCL [poly(ethylene glycol) block-poly(caprolactone)] polymeric micelles Methoxy poly(ethylene glycol) palmitate polymeric micelles	Ma et al., 2008 Sahu et al., 2008
Nanoemulsions	i) Greater stability to droplet aggregation and gravitational separation; (ii) Higher optical clarity; and, (iii) increased oral bioavailability	b-Carotene-based nanoemulsion b-Carotene-based nanoemulsion	Kong et al., 2011 Yuan et al., 2008
Liposomes	Since liposome surrounds an aqueous solution inside a hydrophobic membrane, it can be used delivery vehicles for hydrophobic molecules (contained within the bilayer) or hydrophilic molecules (contained in the aqueous interior)	Cationic lipid incorporated liposomes modified with an acid-labile polymer hyper-branched poly(glycidol) (HPG)	Yoshizaki et al., 2014
Inorganic NPs	They display good encapsulation capability and their rigid surfaces allow controlled functionalization	Mesoporous silica nanoparticles	Tang et al., 2012

II) Organic nano polymers

In addition to large number of synthetic nano-polymers developed, organic nano-biopolymers developed, from variety of biological materials e.g. cell wall of plants or milk protein are reported to working well. They have been shown to enhanced property like (1) uptake (2) absorption and (3) bioavailability in the body. In addition, they are beneficial in terms that they are internalized, degraded easily and releases nutraceuticals inside the intestines only, for example, tuna fish oil rich in omega-3 fatty acid can be delivered safely (Keogh et al. 2001; Augustin and Sanguansri 2009)(Chen and Subirade 2006).

III) Organic carotene/lycopene based nano-particles

In fighting against malnutrition nano-packaging of food additives and supplements may be highly beneficial. Recent work regarding delivery of vitamin A and E, isoflavones, beta-carotene, glutens, omega-3 fatty acids and coenzyme-Q10 using tomato carotenoid lycopene have shown good

Table 3: Relevant properties of food grade proteins commonly used in the synthesis nano and micro carriers (Santiago Castro 2016).

Protein	Source	Conformation	MW(kDa)	pI
BSA	Bovine	Globular	66.5	4.7
Alpha casein	Milk	Rheomorphic	23.0	4.1
Beta Casein			24.0	4.5
Gamma Casein			19.0	4.1
Kappa Casein				5.8-6.0
Gelatin	Animal or fish	Linear	100(monomer)	7.0-9.4
Ovoalbumin	Egg white	Globular	45.0	4.5-4.7
Soy glycinin	soybean	Globular	320(hexamer)	5.0
Beta-lactoglobulin	Whey Protein	Globular	18.4	4.8-5.1
Lactoferrin	Whey Protein	Globular	93.0	8-9
Zein	Corn	Globular	24.0	6.2

results (Hoppe et al. 2003). Carotene/lycopene nanoparticles is now accepted as (GRAS) 'generally recognized as safe' for its use in food (Centre for Food Safety and Applied Nutrition [CFSAN] 2005) (Batz et al. 2005).

iv) Casein micelle

Various milk proteins such as lactoferrin, beta casein, casein micelle (CM) or bovine serum albumin (BSA) have been used for the preparation of conjugated nanoparticles effective for *in-vivo* delivery of many useful components (Zimet and Livney 2009).

Casein micelle (CM) is reported to be highly effective in delivering *of* probiotics, Ca^{++}, Mg^{++} and other ions including phosphate (Chen and Subirade 2006; Augustin and Sanguansri 2009). Casein micelle has advantages as they self induce immobilization of any bioactive compounds after addition of rennet or acid and enzyme transglutaminase. Such kind of self assembly or co-assembly is useful in immobilization of nutraceuticals or bioactive components e.g. curcumin packaging for cancer therapy (Sahu et al. 2008).

Oral drug delivery via casein micelle, makes them better accessible to digestive enzymes and makes them better sustainable in stomach because of presence of proline. In addition casein micelle, provide better sustainable protection against UV radiations to packaged nutraceuticals, vitamins and other organic food components from any oxidation and deterioration (Semo et al. 2007). It also improves bioavailability of carotenoids, phytosterols and antioxidants because of amphipathic nature that helps in dispersion well when packed with functional ingredients e.g (Chen and Subirade 2006). Further, various milk components allow self assembly via micelle formation (10^{14}–10^{16} micelles/ml milk) helpful in nutraceuticals delivery. Globular proteins in milk further assists in better self assembly due to disulfide bridges present naturally (in milk 17 disulphide bridges; while beta lactalbumin had 2 disulphide bridges).

v) Hydrogel microsphere

Other biological materials used for making hydrogel nano-particles are alginate based capsules, chitosan pectin complex, polylactide (PL6a), microsphere polyglycolic acid, dl-lactic acid, starch based capsules. All of them are bio-degradable.

vi) Liposome phospholipid based hydrogel microsphere

Liposome phospholipids are also used to entrap useful drugs and bioactive compounds, and are generally recognized as safe (Mudshinge et al. 2011). Such nanospheres are prepared in case of polyacrylamide grafted guar gum hydrogel microsphere. Various, cross linking agents (such as increased concentration of glutaraldehyde) may further effect the release of diffusing materials. Various inducers such as heat, ultrasound, light and other physical factors such as pH, enzymes, induces self-assembly of liposome phospholipids to form nanoparticles. The release of preservatives here depends on the presence of water and quality of encapsulation and was reported upto 20-40% (Cherukuri et al. 1991). Viscosity

Table 4: Edible nano-coating and Food additives (Pérez-Gago et al. 2010).

Edible coating material	Antimicrobial	Antioxidant	Anti-softening	Nutraceuticals
Made up of Alginate	Essential oils	Calcium chloride	Calcium lactate	Probiotic
	Malic acid	N-Acetyl-Cysteine	Calcium chloride	
	Potassium sorbate	Glutathione		
	Vanillin			
Made up of Apple Puree	Essential oils	Ascorbic acid	Calcium chloride	-
	Vanillin	Citric acid		
Cellulose derivatives	Potassium sorbate	Ascorbic acid	Calcium chloride	
	Sodium benzoate	TBHQ*		
	Trans-cynnamaldehyde vanillin			
Carrageen		Oxalic acid	Calcium chloride	-
		Ascorbic acid		
		Cysteine		
		Citric acid		
Caseinate	Trans-cynnamaldehyde	-	calcium chloride	Calcium
				Vitamin E
Chitosan	Chitosan	Chitosan	calcium chloride	Calcium
	Vanillin			Zinc
				Vitamin E
Gellan	-	Ascorbic acid	Calcium chloride	Probiotic
		N-Acetyl-Cysteine		
		Glutathione		
Maltodextrin	-	ascorbic ac	-	-
Pectin	Trans	N-Acetyl-Cysteine	Calcium chloride	-
	cinnamaldehyde	Glutathione		
Starch	Chitosan	-	-	
Soy Protein	Potassium sorbate	Ascorbic acid	Calcium chloride	
	Sodium benzoate	TBHQ*		
Whey Protein	Trans	Citric acid	Calcium chloride	Calcium
	cynnamaldehyde	Ascorbic acid		Vitamin E
		Oxalic acid		
		Hexylresorcinol		
		Cysteine		

plays an important role in the release of packed organic foods such as nutraceuticals and vitamins in the body. Besides viscosity, dissolution property also increases the flavor, aroma or sweetness in packed items such as chewing gum (Akbarzadeh et al. 2013). In food preservation, encapsulated antimicrobials agents and acids like organic acid, citric acid, ascorbic acid and lactic acid can be boon in food safety.

Table 5: Loaded molecules in carriers of protein origin (Santiago Castro 2016).

Nanocarrier	Bioactive
Beta lactoglobulin	Folic acid, curcumin, polyphenol extracts of teas, coffee, cocoa, oleic and linoleic acid, naringenin
Beta lactoglobulin (variants A, B, C)	Retinol and EGCG
Preheated Beta lactoglobulin	Naringenin and narangin
Beta lactoglobulin, BSA and alpha-lactaalbumin	Folic acid
Ovalbumin	Caffeine, theophyline, diprophylline
Ovalbumin and lysozyme	Tea polyphenol
β-conglycinin	Vitamin D
β-conglycinin	Curcumin
Canola protein and pea protein isolates	Ketones
Gliadin and Zein	Resveratrol
Pretreated Beta lactoglobulin	Linolenic acid
Hydrolysed Beta lactoglobulin	Linolenic acid
Isostatic high pressure Beta lactoglobulin	Retinol
Preheated Ovalbumine	Linolenic acid
Pretreated Beta lactoglobulin	Linolenic acid
Beta lactoglobulin/sodium alginate	Folic acid, curcumin, ergocalciferol, β carotene
Sodium caseinate – gum Arabic	EPA/HDA

vii) Soy protein based Nano-hydrogel

Now a days, nano-hydrogel have been made for packaging of riboflavin. These hydrogel are made up of soy protein and gel has many advantages. The release of riboflavin is reported to be faster in gastric conditions by the activity of various proteolytic enzymes such as trypsin, chymotrypsin and elastase (Maltais et al. 2010). Beta-cyclodextrin capsules entrapped with antifungal volatile thyme essential oil (TOL) requires only high Relative humidity(RH) which is beneficial and is less complicated.

4. NANO FILMS & EDIBLE COATINGS

"Dupont" has developed Dupont light stabilizer 210 nano film to save perishable foods items from UV rays. Similarly Nano liposomes based hybrid encapsulation structures utilizing β-carotene loaded were developed to improve the photo stability of the antioxidants. (de Freitas Zômpero et al. 2015). El Amin (2006) reported some antimicrobial films, reported to improve the shelf life of food and dairy products, available in the market with enhanced mechanical and thermal properties with improved level of safety and functionality. Weiss et al. (2006) reported that Nano laminates and edible coatings are important for the food and dairy industries. These nano laminated coatings can be developed from proteins, polysaccharides, lipids by using simple steps such as dipping and washing (Weiss et al. 2006).

5. NANOTECHNOLOGY IN FOOD PACKAGING: SMART NANO-PACKAGING WITH ANTIBACTERIAL PROPERTIES

Smart food packaging involve sensors which foretells about deterioration /spoiling of packaging materials and packed items and also releases various items including preservative such as flavors, antimicrobials, colors or nutritional supplements into the food at the start of spoiling and also improves heat resistance property (Brody 2003; De Azeredo 2009). Nano-based "smart" and "active" food packaging is better than the conventional packaging methods as it provides packaging material with enhanced mechanical strength, barrier properties and also incorporates antimicrobial films to sense for pathogen detection and giving alarm signals

Table 6: Problems implications and effective delivery system (Tiwari and Takhistov 2012).

Problematic	Implications	Effect of delivery system
Reduced solubility, e.g. CoQ10	mostly nutraceutical may precipitate due to hydrophobic nature so delivery issue	Liposome can be used
Degradation in heat, acid and light,e.g. lycopene	Loss of activity (cis/trans Isomerization)	Coating requires
Hydrophobic nutraceuticals, e.g. ECG and EGCG	Difficult to incorporate in food Systems	hydrogels is effective
Vulnerable to oxidation, e.g. omega fatty acid	Oxidative products are harmful	Coacervates can be advantage that increases thermal stability and protect against oxidation
Degradation, e.g. theaflavins	Loss of activity to metabolization by enzyme	Delivery system provides protection against such degradations
Rapid breakdown, e.g. flavonoids	Denaturation and loss of activity, e.g. loss due to pH	dendrimers can protect against premature degradation

to the consumers regarding the safety status of food (Mihindukulasuriya and Lim, 2014)(Sandetskaya et al. 2013). Further, nano structures helped a great deal in enhancements of properties, for example, optical, chemical, organic and electrical properties (Roco 2011).

Fabrication of nanomaterials with nano-biosensors had helped a considerable measure in gathering of information related to food spoilage or in other words to consumers in regard to advanced safety information before their genuine damage because of spoilage, which may occur due to amid transportation or defective storage. Nano carriers had been developed for enhanced delivery of nutraceuticals and probiotics, while nano coatings have self-cleaning properties which enables them to maintain hygienic conditions, while some food of plastic/nano-silver composite and nano-coatings containing metal oxide (nano-zinc oxide) acts as antimicrobial agents. Recently, improved packaging properties is because of ENP (engineered nanoparticles) based nanoparticles.

Nanocomposites can be used as an active material for improved food packaging and also as a material coating.(Pinto et al., 2013). Exploring the antimicrobial properties of organic compounds like essential oils, organic acids and bacteriocins and their use in polymeric matrices was studied by many researchers but the problem with these compounds were that during food processing steps they require extreme temperature and pressure conditions and these compounds are highly sensitive to these conditions (Gálvez et al.,2007; Schirmer et al., 2009).But with the application of inorganic nanoparticles, a strong antibacterial activity was achieved even in low concentrations and was more stable in extreme conditions. So use of these nanoparticles is of great interest in antimicrobial food packaging. (Soares et al., 2009).

Nanoparticles reported to have antibacterial properties are silver, copper, chitosan and metal oxide nanoparticles like titanium oxide or zinc oxide (Bradley et al., 2011; Tanet al., 2013; Figure 1). Not only nanoparticles have application in antimicrobial food packaging but nanocomposites and nanolaminates are used in food packaging to extend the shelf life by providing a barrier from extreme thermal and mechanical shock.

To improve the properties of polymer composites, inorganic or organic fillers are being used due to which more resist packaging material is developed and is cost effective also (Sorrentino et al.,2007). Using inert nanoscale fillers such as clay and silicate nano-platelets, silica (SiO2) nanoparticles, chitin or chitosan into the polymer matrix renders it lighter, stronger, fire resistant with better thermal properties (Duncan, 2011; Othman, 2014).Nanocomposite films have antimicrobial property which is prepared by impregnating the fillers (nanoparticles in nanometric range) into the polymers. It has advantage as these fillers possess good structural integrity and have good barrier properties (Rhim 2004).A very good review has been written over food nanosensors in the miniaturized systems for advanced analytics and diagnostics by Kuhlmeier et al.(Kuhlmeier et al. 2012). A self cleaning device has been developed which not only is dust repellent but also antimicrobial by CTC nanotechnology (GmbH), Merzig, Germany. NiO/TiO2 composite nanofibers is reported with antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Salmonella typhimurium* (Amna et al. 2011).

Table 7: Nanoparticles employed for the detection of foodborne pathogens.

Nanoparticles	Pathogens	Detection limit	References
Gold nanoparticle	*Salmonella enterica serotype Typhi*	98.9 CFU/mL	Vikesland, P. J., & Wigginton, K. R. (2010).
Gold/silicon nanorod	*Salmonella enterica serotype Typhi*; Respiratory syncytial virus	Not reported	Dungchai, W., Siangproh, W., Chaicumpa, W., Tongtawe, P., & Chailapakul, O. (2008).
Gold nanorod	*Escherichia coli* O157:H7	1–10 CFU/mL	Fu, J., Park, B., Siragusa, G., Jones, L., Tripp, R., Zhao, Y., & Cho, Y. J. (2008).
Quantum dot	*Salmonella enterica serotype Typhi*, *E. coli*O157:H7, *Listeria monocytogenes*	10^3–10^6 cells/mL	Tully, E., Hearty, S., Leonard, P., & O'Kennedy, R. (2006).
Magnetic bead/ quantum dot	*E. coli* 0157:H7	10^3 CFU/mL	Yang, L., & Li, Y. (2006).
RuBpy doped silica	*E. coli* O157:H7	1 cell/mL	Su, X. L., & Li, Y. (2004).
Single walled carbon nanotube	*E. coli*	Not reported	Zhao, X., Hilliard, L. R., Mechery, S. J., Wang, Y., Bagwe, R. P., Jin, S., & Tan, W. (2004).
Magnetic nanoparticle	*E. coli* O157:H7, *S. aureus, S. epidermidis*	10^4 CFU/mL, 8 CFU/mL, 10 CFU/mL	Zhao, X., Hilliard, L. R., Mechery, S. J., Wang, Y., Bagwe, R. P., Jin, S., & Tan, W. (2004).
Immunomagnetic liposome nanoparticle	*Cronobacter sakazakii*	10^3 CFU/mL	Shukla, S., Lee, G., Song, X., Park, S., & Kim, M. (2016).
Aptamer conjugated gold nanoparticles	*Salmonella typhimurium*	10^4 CFU/mL	Oh, S. Y., Heo, N. S., Shukla, S., Cho, H. J., Vilian, A. E., Kim, J., ... & Huh, Y. S. (2017).
Liposome nanoparticles	*Salmonella typhimurium*	10^2 CFU/mL	Zhou, L., Lv, S., He, G., He, Q., & Shi, B. I. (2011).

6. NANOTECHNOLOGY IN FOOD PROCESSING

Wastage of food is common occurrence due to spoilage of food. In this regard it's important to use nano technology to improve not only shelf-life properties but also improving the taste, texture, maintaining the original texture of the food. Nano encapsulation using nano vehicles to deliver antimicrobial component in processed food is major focus in development to improve shelf-life as well as its protection from UV, moisture, heat and other factors that promote spoilage. For example ferritin trapped rutin has found better application for protection of food against several spoilage. (Yang et al., 2015). To enhance flavor in food SiO2 nanoparticles are commonly used (Dekkers et al., 2011).

A) Food processing sector

Processing of foods involve use of nano-food ingredients/ additives, for improved organoleptic properties such as tastes, textures, and sensory properties (Chaudhry et al. 2010, 2011; Chaudhry and Castle 2011). For example Nano encapsulation of nutraceuticals, had improved their solubilization, delivery, and color in food systems (Ravichandran 2010; Mura et al. 2014).

In meat processing industrynanosystem can play important role but maintaining stability of nano systems and delivery products is a basic challenge in meats

industry and other unknown associated health risks due to use of nanomaterials. Other challenges may be their public acceptance on the ground of economics and country regulation of food processed its persistence and toxicity associated. Low fat nanostructure ice-creams and spreads equivalent to the full fat alternatives claims to offer a healthy options to the consumers.

b) Improving shelf life

Improving shelf life is another arena where application of nanotechnology is implicated in these sector. Food safety is a major concern and is crucial factor in the growth of developing countries worldwide. Food packaging using nano materials can improve the coatings and can increase shelf life if have antibacterial property thus increases food safety, can detect microbes and is beneficial in-term of good barrier properties for example silver-based antibacterial hybrid materials (Sekhon 2010). This can be applied over beef meat or any meat type with better safety features since major bacterial count lower down than normal one using such antibacterial Nano-materials. TiO2 nano-material,(Wang et al. 2014b) Boron-doped TiO2 (B/TiO2) nano-materials (Xue et al. 2013) metal oxide nanoparticles (NPs) (Hajipour et al. 2012) ZnO nanoparticles (Shi et al. 2014) are reported to be active against broad spectrum of bacteria. Other such nanoscale materials are cadmium selenide/telluride, magnesium oxide, gold, alginate, chitosan, antimicrobial peptides fullerenes, as well as carbon nanotube (Bata-Vidács et al. 2013).

Various food products get spoiled easily due to lack of proper food packaging, therefore some **antibacterial** paper based Nano coating helped a lot in this regard e.g. Antifungal active paper packaging where, cinnamon oil used along with solid wax paraffin for active coating also is helpful in bakery products. Rojas et al, used oregano oil and apple puree, for creating edible food films also are capable of killing to *E. coli* bacteria.(Rojas-Graü et al. 2007; Rodriguez-Lafuente et al. 2010).

Recently more interest have been there in various edible coating over foods made up of polysaccharides such as starch (Osés et al. 2009a, b, c) corn (Psomiadou et al. 1996) carboxymehylcellulose (CMC) and methyl cellulose (MC) (Pérez-Esteve et al. 2013), sodium caseinate films reinforced with cellulose derivatives (Pereda et al. 2011), from cress seed carbohydrate gum (Correa et al. 2010) High methoxyl pectin–methyl cellulose films with antioxidant activity (Pérez et al. 2013) from psyllium seed (Plantago ovata Forsk), edible film obtained (Ahmadi et al. 2012) cyclodextrin–polysaccharide hydrogels as antifungal devices (Lopez-Montero et al. 2009). Some form of waxy coating over apples and cheeses helps them in saving from degradations and such coating have been used over wide diversity of foods such as meats, fruits, vegetables, cheese, chocolate, bakery products, candies, and French fries (Morillon et al. 2002; Cagri et al. 2004; Rhim 2004). Its has following benefits.

(1) It can work against lipid, moisture, and gas barriers.
(2) Improve the textural properties of foods.
(3) Can aid as carriers of functional agents such as flavours, colours, antioxidants, antimicrobials and nutrients.
(4) Can also upsurge the shelf life of factory-made foods after opening of the packets.

An edible antibacterial nano-coating for bakery goods has been developed by the U.S. Company Sono-Tec Corporation (Amin et al. 2006).A few nanomaterials such as silver nanoparticle is advantageous which is also a antibacterial agent. Nano encapsulation of preservative is considerable for better health.(Chaudhry et al. 2011). Besides this some more example of permitted food additives are E551, SiO2, and TiO2, E171, (EFSA, 2009) which can be delivered at micro reduced concentration for better health.

Increasing the shelf life of meat, is major requirements in meat processing industry which currently suffer from various challenges related to food safety and quality of meat after longer preservation. Conventional preservation techniques involve addition of various additive such as salts and preservative chemicals. Further adding large quantity of salt poses problems due to various health issues linked such as high B.P., cardiovascular diseases (Weiss et al. 2006, 2010). Microencapsulation helps in improving stability, storage , distribution and texture of foods in (Coles and Frewer 2013) masking bad odor of fish oil (Chaudhry et al. 2011). Also it may result in extended shelf life, prevents food borne diseases and also enhances organoleptic properties (Donsì et al. 2011). Some recently used nano-encapsulated materials such as liposomes, protein based carriers or micelles have been used in many applications such as for masking taste of certain additives and ingredients, to protect them from ruining during processing. Such as tomato carotenoid lycopene, food additives, ascorbic acid, citric acid, benzoic acid, and supplements such as isoflavones, vitamins A and E, ß-carotene, omega-3 fatty acids, lutein, coenzyme-Q10.

c) Improved Functional food delivery

Intervention of nanotechnology has not only increased the effect of over viability and thus enhances more pronounced effect of probiotics since probiotics protection

against pathogen depends on number of viable lactobacillus cells in intestine more the number of viable cells and more occupation of intestinal area, has benefits that pathogen has less surface area to occupy and presence of antimicrobial protein leads them to easy clearance. Thus probiotic is an important field of functional food (Cook et al. 2012).

Encapsulation of probiotic strain enables them to resist more against gastric juices, bile juice, and one such product have been patented in recent past (Chung et al. 2010) where triple coating was done. The first coating was protein coat made up of soya isolate in presence of protease, polysaccharides (xanthan gum) and final coating was done using nanoparticle made-up of solid lipid and size 100 – 200 nm and was safe to add in fermented milk. In addition germicidal coating of LAB over condoms by nano-composing (titanium dioxide, zinc oxide, chitin beads and chitosan beads). Various commonly used probiotics microbes are *Lactobacillus salivarius, Lactobacillus acidophilus, Saccharomyces boulardii, Saccharomyces thermophilus and Bifidobacterium* species that have various function such as (1) Digestion of food, (2) Fermentation of sugars, (3) Prevent tumour formation,(4) Stimulate vitamins and antibiotics production and (5) inhibit various pathogens.

d) Food fortification

Food fortification practices is related to link with improving important health measures in order to prevent deficiencies of vitamin A, Iron, Folic acid and sometimes Iodine. But food fortification is very expensive, highly skilled manpower is required because of costly instruments involved using conventional methods. Also risk of overdosing and toxicity remains besides problems of suitable carrier, keeping up constant doses, the only solution is the use of nanotechnology where concept of designer food exists in the form of food additives, anti foaming agents for beer, as colour additive in lemonades, as encapsulated vitamins in dietary system and low fat food using Micelle system. (Tiwari R, Takhistov P (2012).

7. PARAMETERS USED FOR EFFECTIVE RELEASE AND DELIVERY MECHANISM

As nano carrier, micelles and vesicles have been extensively studied for controlled release of food, at different pH, temp, moisture and shear. Another way of release mechanism have been studied are fracturation (Yavlovich et al. 2011) whereas enzyme activated vesicular system have been used. Mostly nano carrier made up of encapsulated (volatile) carbohydrate such as cross linked polyacrylamide, chitosan ethyl cellulose complex, and grafted guar gum hydrogel microsphere. Release of encapsulated bioactive compound depends on physical and chemical property of encapsulate. There are various mode of release of nano foods by nano carrier such as by diffusion (Soppimath et al. 2001) dissolution and biodegradation (de Vos et al. 2010). Nutraceuticals can be defined as food or food ingredients that has medical importance which includes many processed foods, such as cereal soup and beverages and delivery of such component may be useful in term of delivery, effectiveness by using nanoparticle such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, emulsions, micelles and poly (lactic-co-glycolic acid) (PLGA) (Wang et al. 2014a). Intralipid® was first FDA approved intravenous fat emulsion based nanoparticles for delivery of essential fatty acids in 1972 made up of egg phospholipid soy bean oil and glycerin. (McNiff 1977).

Size is the most important parameter decisive in interactions of nanoparticles and living systems (Berhanu et al. 2009; Sayes and Warheit 2009) The size of the nanoparticles can be regulated by the methods used for their synthesis. The synthesis of nanoparticles at the laboratory and industrial scale varies in different institutions.

Few of the commonly used methods are spray – drying process, sol gel technique, micro emulsion processing. For the synthesis of ENMs, sol gel technique is employed due to its simplicity and flexibility in controlling the final properties (Kumar and Dhawan 2013).

Most of the vitamins losses their property after high temperature, moisture, oxygen, light, and pH. Thus various nano based emulsion can solve this problems. Based on O/W emulsion various commercial emulsion have been established for delivery of bioactive compounds such as vitamin A,D,E,K ; omega-3 fatty acids, carotenoids, phytosterols, flavonoids Curcumin and other phytochemicals in the name of Vitalipid ®(McClements et al. 2007; Tiwari and Takhistov 2012).

Nano particle may acts as protective shield and could be able to prevent loss of various important bioactive compounds for example curcumin, is very effective in suppressing apoptosis induces in near by cells after chemotherapy of tumors. Their nano delivery will not only increase the effect by enhancing the delivery and also due to Nano shield their degradation will be enhanced. It has been observed that bio absorption of these molecule can be increased by attaching specific ligands to nanoparticles, which helps them attaching in intestine. For example attaching BSA/lectine to PVM/MA nanoparticles increases attachments incredibly and further intestinal pH and other factors helps them

in activation and targeted delivery. Various compatible nanoparticle exist such as Silica, alumina titanium and Ceramic-based nanoparticles.

8. HEALTH IMPACT AND SAFETY ISSUES

Monitoring of nanomaterial over negative health impact is essential for food safety (Cushen et al. 2012) since nano materials enters through oral route in GIT and then into circulation and many vital organs such as liver and spleen (Silvestre et al. 2011) and also metals used in nanomaterials may be persistence (Chaudhry and Castle 2011). For e.g. silver nanoparticles (AgNPs) have reported to damage liver of rats while ZnO nanoparticles are toxic to human epidermal cells (Sharma et al. 2009).

A number of advantages of using nanoparticles has been discussed but concern is over using these particles and their health impact since these nanoparticles can cross the blood brain barrier. For example silica nanoparticles has several applications but they show cytotoxic effect to lung (Athinarayanan, Periasamy, Alsaif, Al-Warthan, & Alshatwi, 2014)Therefore, assessing the concentration aggregation in several organs is important in respect to health impact. Some case study for impact of silver nanoparticles over health has found to vary from case to case (Mahler et al., 2012)Various regulatory authorities are also developing technology to assess their impact over health and environment before approval of their commercial release. Monitoring of nanomaterial over negative health impact is essential for food safety (Cushen et al. 2012) since nano materials enters through oral route in GIT and then into circulation, and may vital organs such as liver and spleen (Silvestre et al. 2011) and also metals used in nanomaterials may be persistence (Chaudhry and Castle 2011). For e.g. silver nanoparticle (AgNPs) reported to damage liver of rats while ZnO nanoparticle is toxic to human epidermal cells observed that (Sharma et al. 2009).

Various reviews focused on nano food safety and their impact (Sonkaria et al. 2012). More concern is over negative impact of nanotechnologies on the environment and health. Among reports of several survey shows that still people have a lot of fear about nanofoods toxicity since it can cross blood brain barrier. Smart materials, for smart delivery is the attractive option in form of nanomaterials for different uses in nano food industries. Nanomaterials such as nanopowders, nanotubes, nano-fibers, quantum dots, and metal and metal-oxide nanoparticles are of great applications in nano foods thus, produced largely owing to their smart features in term of large surface area, high activity, solubility chemical properties, and degree of agglomeration can cross cell boundaries or pass directly from the lungs via the blood stream or ultimately they reach many organs. This is a higher threat than the same mass and material of larger particles (Siegrist et al. 2007). Though many exciting novelties exist in the different food realm such as better delivery and longer shelf-life, solubility of vitamins, enhance flavor etc.

The attitude of consumers mainly European consumer attitudes is totally negative towards nanotechnology foods, but positive with those products if natural additives" are added and have positive health benefits (Bredahl 2001; Grunert et al. 2004).

9. CONCLUSION

Nanotechnology has carved a significant niche in food industry and is ready to extend improved nanomaterials for functional food designing in the form of smart packaging with targeted delivery. Further it has scope of enhanced safety for consumers with delivery in very small amount. Also it has a larger number of advantages than damage as conjectured however on a condition that all new organic nanomaterials ought to be utilized. Despite there are number of beneficial applications, but public fear remains about the associated risk using nanomaterials on health. Consequently, some guidelines have been issued for health hazard evaluation and safe delivery of the food additives, (for example, salt, sugar, fat, artificial colors and preservatives) with minimum migration. Since no agency had declared nano-packaged food risk proof so risk assessment data is required with suitable trials methodology for accurate detection and monitoring tools.

10. REFERENCES

1. Ahmadi, R., Kalbasi-Ashtari, A., Oromiehie, A., et al. (2012). Development and characterization of a novel biodegradable edible film obtained from psyllium seed (Plantago ovata Forsk). *J Food Eng.* 109:745–751.
2. Akbarzadeh, A., Rezaei-Sadabady, R., Davaran, S., et al. (2013). Liposome: classification, preparation, and applications. *Nanoscale Res Lett.* 8:102. https://doi.org/10.1186/1556-276X-8-102.
3. Amin, M. N., Kaneco, S., Kitagawa, T., et al. (2006). Removal of arsenic in aqueous solutions by adsorption onto waste rice husk. *Ind Eng Chem Res.* 45:8105–8110.
4. Amna, T., Hassan, M. S., Yousef, A., et al. (2011). Inactivation of Foodborne Pathogens by NiO/TiO2 Composite Nanofibers: A Novel Biomaterial System.

Food Bioprocess Technol. 6:988–996. https://doi.org/10.1007/s11947-011-0741-1.

5. Augustin, M. A. & Sanguansri, P. (2009). Nanostructured materials in the food industry. *Adv Food Nutr Res.* 58:183–213.
6. Avella, M., De Vlieger, J. J., Errico, M. E., et al. (2005). Biodegradable starch/clay nanocomposite films for food packaging applications. *Food Chem.* 93:467–474.
7. Baeumner, A. (2004). Nanosensors identify pathogens in food.
8. Basavaraja, S., Balaji, S. D., Lagashetty, A., et al. (2008). Extracellular biosynthesis of silver nanoparticles using the fungus Fusarium semitectum. *Mater Res Bull.* 43:1164–1170. https://doi.org/10.1016/j.materresbull.2007.06.020.
9. Bata-Vidács, I., Adányi, N., Beczner, J., et al. (2013). Nanotechnology and Microbial Food Safety.
10. Batz, M. B., Doyle, M. P., Morris Jr, G., et al. (2005). Attributing illness to food. *Emerg Infect Dis.* 11:993–9.
11. Berger, M. (2008). Food nanotechnology-how the industry is blowing it.
12. Berhanu, D., Dybowska, A., Misra, S. K., et al. (2009). Characterisation of carbon nanotubes in the context of toxicity studies. *Env Heal.* 8:S3.
13. Bhattacharya, S., Jang, J., Yang, L., et al. (2007). BioMEMS and nanotechnology-based approaches for rapid detection of biological entities. *J Rapid Methods Autom Microbiol.* 15:1–32.
14. Bouwmeester, H., Dekkers, S., Noordam, M. Y., et al. (2009). Review of health safety aspects of nanotechnologies in food production. *Regul Toxicol Pharmacol.* 53:52–62. https://doi.org/10.1016/j.yrtph.2008.10.008.
15. Bredahl, L. (2001). Determinants of Consumer Attitudes and Purchase Intentions With Regard to Genetically Modified. *J Consum Policy.* 24:23–61. https://doi.org/10.1023/A:1010950406128.
16. Brody, A. L. (2003). " Nano, Nano" Food Packaging Technology. *Food Technol.* 57:52–58.
17. Cagri, A., Ustunol, Z. & Ryser, E. T. (2004). Antimicrobial edible films and coatings. *J Food Prot.* 67:833–848.
18. Chau, C.-F., Wu, S.-H. & Yen, G.-C. (2007a). The development of regulations for food nanotechnology. *Trends Food Sci Technol.* 18:269–280.
19. Chau, C.-F., Wu, S.-H. & Yen, G.-C. (2007b). The development of regulations for food nanotechnology. *Trends Food Sci Technol.* 18:269–280.
20. Chau, C. F., Wu, S. H. & Yen, G. C. (2007c). The development of regulations for food nanotechnology. *Trends Food Sci Technol.* 18:269–280. https://doi.org/10.1016/j.tifs.2007.01.007.
21. Chaudhry, Q. & Castle, L. (2011). Food applications of nanotechnologies: an overview of opportunities and challenges for developing countries. *Trends Food Sci Technol.* 22:595–603.
22. Chaudhry, Q., Castle, L. & Watkins, R. (2011). Nanomaterials in food and food contact materials–potential implications for consumer safety and regulatory controls. *Nanotechnol agri-food Sect.* 1:3.
23. Chaudhry, Q., Castle, L. & Watkins, R. (2010). Nanotechnologies in food. *Royal Society of Chemistry.*
24. Chen, H., Weiss, J. & Shahidi, F. (2006). Nanotechnology in nutraceuticals and functional foods. *Food Technol.* 60:30–36.
25. Chen, H., Zuo, X., Su, S., et al. (2008a). An electrochemical sensor for pesticide assays based on carbon nanotube-enhanced acetycholinesterase activity. *Analyst.* 133:1182–1186. https://doi.org/10.1039/b805334k.
26. Chen, L. & Subirade, M. (2006). Alginate–whey protein granular microspheres as oral delivery vehicles for bioactive compounds. *Biomaterials.* 27:4646–4654.
27. Chen, S. H., Wu, V. C. H, Chuang, Y. C. & Lin, C. S. (2008b). Using oligonucleotide-functionalized Au nanoparticles to rapidly detect foodborne pathogens on a piezoelectric biosensor. *J Microbiol Methods.* 73:7–17. https://doi.org/10.1016/j.mimet.2008.01.004.
28. Cherukuri, S. R., Chau, T. L., Raman, K. P. & Orama, A. M. (1991). Multiple encapsulated flavor delivery system and method of preparation. *Google Patents.*
29. Chung, M. J., Kim, D. M., Kim, J. E. & Lee, G. S. (2010). Method of preparing triple-coating lactic acid bacteria and nano particle coating method, triple-coating lactic acid bacteria prepared thereby and article comprising the same.
30. Cobb, M. D. (2005). Framing effects on public opinion about nanotechnology. *Sci Commun.* 27:221–239.
31. Cobb, M. D. (2011). Creating informed public opinion: citizen deliberation about nanotechnologies for human enhancements. *J Nanoparticle Res.* 13:1533–1548.
32. Coles, D. & Frewer, L. J. (2013). Nanotechnology applied to European food production–a review of ethical and regulatory issues. *Trends Food Sci Technol.* 34:32–43.
33. Consultancy, H. K. (2004). Nanotechnology in food and food processing industry worldwide. *Unpubl study, Tübingen.* 35.

34. Cook, M. T., Tzortzis, G., Charalampopoulos, D. & Khutoryanskiy V. V. (2012). Microencapsulation of probiotics for gastrointestinal delivery. *J Control Release.* 162:56–67. https://doi.org/10.1016/j.jconrel.2012.06.003.

35. Correa, M. J., Añón, M. C., Pérez, G. T. & Ferrero, C. (2010). Effect of modified celluloses on dough rheology and microstructure. *Food Res Int.* 43:780–787.

36. Cushen, M., Kerry, J., Morris, M., et al. (2012). Nanotechnologies in the food industry–Recent developments, risks and regulation. *Trends Food Sci Technol.* 24:30–46.

37. De Azeredo, H. M. (2009). Nanocomposites for food packaging applications. *Food Res Int.* 42:1240–1253.

38. de Freitas Zômpero, R. H., López-Rubio, A., de Pinho, S. C., et al. (2015). Hybrid encapsulation structures based on ß-carotene-loaded nanoliposomes within electrospun fibers.

39. de Vos, P., Faas, M. M., Spasojevic, M. & Sikkema, J. (2010). Encapsulation for preservation of functionality and targeted delivery of bioactive food components. *Int Dairy J.* 20:292–302.

40. Donsì. F., Annunziata, M., Sessa, M. & Ferrari, G. (2011). Nanoencapsulation of essential oils to enhance their antimicrobial activity in foods. *LWT-Food Sci Technol.* 44:1908–1914.

41. Doyle, M. E. (2001). FRI BRIEFINGS.

42. Duncan, T. V. (2011). Applications of nanotechnology in food packaging and food safety: Barrier materials, antimicrobials and sensors. *J Colloid Interface Sci.* 363:1–24. https://doi.org/10.1016/j.jcis.2011.07.017.

43. Dungchai, W., Siangproh, W., Chaicumpa, W., Tongtawe, P. & Chailapakul, O. (2008). Salmonella typhi determination using voltammetric amplification of nanoparticles: a highly sensitive strategy for metalloimmunoassay based on a copper-enhanced gold label. *Talanta*. 77(2), 727-732.

44. ElAmin, A. (2006). Nanotech database compiles consumer items on the market.

45. Fletcher, N. & Bartholomaeus, A. (2011). Regulation of nanotechnologies in food in Australia and New Zealand. *Int Food Risk Anal. J.* 2:33–40.

46. Fu, J., Park, B., Siragusa, G., Jones, L., Tripp, R., Zhao, Y. & Cho, Y. J. (2008). An Au/Si hetero-nanorod-based biosensor for Salmonella detection. *Nanotechnology.* 19(15), 155502.

47. Garber, C. (2006). Nanotechnology food coming to a fridge near you.

48. Gokhale, A. A. & Lee, I. (2014). Recent advances in the fabrication of nanostructured barrier films. *J Nanosci Nanotechnol.* 14:2157–2177.

49. Grunert, K. G., Bredahl, L. & Brunso, K. (2004). Consumer perception of meat quality and implications for product development in the meat sector – a review. *Meat Sci.* 66:259–272. https://doi.org/10.1016/s0309-1740(03).00130-x.

50. Hajipour, M. J., Fromm, K. M., Akbar Ashkarran, A., et al. (2012). Antibacterial properties of nanoparticles. *Trends Biotechnol.* 30:499–511.

51. Heugens, E. H., Wijnhoven, S. W. & Ross, B. L. Technology Sector Evaluation: Agrifood V 1.0 July 2010.

52. Hoppe, P. P., Krämer, K., Van den Berg, H., et al. (2003). Synthetic and tomato-based lycopene have identical bioavailability in humans. *Eur J Nutr.* 42:272–278.

53. Johnston, J. H., Grindrod, J. E., Dodds, M. & Schimitschek, K. (2008). Composite nano-structured calcium silicate phase change materials for thermal buffering in food packaging. *Curr Appl Phys.* 8:508–511. https://doi.org/10.1016/j.cap.2007.10.059.

54. Joshi, K. A., Tang, J., Haddon, R., et al. (2005). A disposable biosensor for organophosphorus nerve agents based on carbon nanotubes modified thick film strip electrode. *Electroanalysis.* 17:54–58. https://doi.org/10.1002/elan.200403118.

55. Keogh, M. K., O'Kennedy, B. T., Kelly, J., et al. (2001). Stability to oxidation of spray-dried fish oil powder microencapsulated using milk ingredients. *J Food Sci.* 66:217–224.

56. Kuhlmeier, D., Sandetskaya, N. & Allelein, S. (2012). Application of nanotechnology in miniaturized systems and its use in medical and food analysis. *Recent Pat Food Nutr Agric.* 4:187–199.

57. Kumar, A. & Dhawan, A. (2013). MANUAL ON CRITICAL ISSUES IN NANOTECHNOLOGY R&D MANAGEMENT.

58. Kumari, A. & Yadav, S. K. (2014). Nanotechnology in agri-food sector. *Crit Rev Food Sci Nutr.* 54:975–984.

59. Lopez-Montero, E., dos Santos J.-F. R., Torres-Labandeira, J. J., et al. (2009). Sertaconazole-loaded cyclodextrin–polysaccharide hydrogels as antifungal devices. *Open Drug Deliv J.* 3:1–9.

60. Malanowski, N., Heimer, T., Luther, W. & Werner, M. (2008). Growth market nanotechnology: an analysis of technology and innovation. John Wiley & Sons.

61. Maltais, A., Remondetto, G. E. & Subirade, M. (2010). Tabletted soy protein cold-set hydrogels as carriers of nutraceutical substances. *Food Hydrocoll.* 24:518–524.

62. McClements, D. J., Decker, E. A. & Weiss, J. (2007). Emulsion-based delivery systems for lipophilic bioactive components. *J Food Sci.* 72:R109–R124.

63. McNiff, B. L. (1977). Clinical use of 10% soybean oil emulsion. *Am J Hosp Pharm.* 34:1080–1086.

64. Milan, B. Ž., Marija, B., Jelena, I., et al. (2013). Nanotechnology and its potential applications in meat industry. *Tehnol mesa.* 54:168–175.

65. Morillon, V., Debeaufort, F., Blond, G., et al. (2002). Factors affecting the moisture permeability of lipid-based edible films: a review. *Crit Rev Food Sci Nutr.* 42:67–89.

66. Mudshinge, S. R., Deore, A. B., Patil, S. & Bhalgat, CM. (2011). Nanoparticles: emerging carriers for drug delivery. *Saudi Pharm J.* 19:129–141.

67. Mura, S., Carta, D., Roggero, P. P., et al. (2014). Nanotechnology and Its Applications in Food and Animal Science. *Ital J Food Sci.* 26:91–102.

68. Nano-enabled packaging for the food and beverage industry – a global technology, industry and market analysis.

69. http://www.innoresearch.net/report_summary.aspx?id=68&pg=107&rcd=FT-102&pd=7/1/2009 .

70. Oh, S. Y., Heo, N. S., Shukla, S., Cho, H. J., Vilian, A. E., Kim, J. & Huh, Y. S. (2017). Development of gold nanoparticle-aptamer-based LSPR sensing chips for the rapid detection of Salmonella typhimurium in pork meat. *Scientific reports*. 7(1), 10130.

71. Osés, J., Fabregat-Vázquez M, Pedroza-Islas, R., et al. (2009a). Development and characterization of composite edible films based on whey protein isolate and mesquite gum. *J Food Eng.* 92:56–62.

72. Osés, J., Fernández-Pan, I., Mendoza, M. & Maté, J. I. (2009b). Stability of the mechanical properties of edible films based on whey protein isolate during storage at different relative humidity. *Food Hydrocoll.* 23:125–131.

73. Osés, J., Niza, S., Ziani, K. & Maté, J. I. (2009c). Potato starch edible films to control oxidative rancidity of polyunsaturated lipids: effects of film composition, thickness and water activity. *Int J food Sci Technol.* 44:1360–1366.

74. Pereda, M., Amica, G., Rácz, I. & Marcovich, N. E. (2011). Preparation and characterization of sodium caseinate films reinforced with cellulose derivatives. *Carbohydr Polym.* 86:1014–1021.

75. Pérez-Esteve, E., Bernardos, A., Martínez-Máñez, R. & M Barat, J. (2013). Nanotechnology in the development of novel functional foods or their package. An overview based in patent analysis. *Recent Pat Food Nutr Agric* 5:35–43.

76. Pérez-Gago, M. B., González-Aguilar, G. A. & Olivas, GI. (2010). Edible coatings for fruits and vegetables. *Stewart Postharvest Rev.* 6:1–14.

77. Pérez, C. D, De'Nobili, M. D., Rizzo, S. A., et al. (2013). High methoxyl pectin–methyl cellulose films with antioxidant activity at a functional food interface. *J Food Eng.* 116:162–169.

78. Psomiadou, E., Arvanitoyannis, I. & Yamamoto, N. (1996). Edible films made from natural resources; microcrystalline cellulose (MCC), methylcellulose (MC) and corn starch and polyols—Part 2. *Carbohydr Polym.* 31:193–204.

79. Ravichandran, R. (2010). Nanotechnology Applications in Food and Food Processing: Innovative Green Approaches, Opportunities and Uncertainties for Global Market. *Int J Green Nanotechnol Phys Chem. 1:P72–P96.* https://doi.org/10.1080/19430871003684440.

80. Rhim, J.-W. (2004). Physical and mechanical properties of water resistant sodium alginate films. *LWT-Food Sci Technol.* 37:323–330.

81. Roach, A., Dunlap, J. & Harte, F. (2009). Association of Triclosan to Casein Proteins Through Solvent-Mediated High-Pressure Homogenization. *J Food Sci.* 74:N23–N29.

82. Robinson, D. K. R. & Morrison, M. J. (2010). Nanotechnologies for food packaging: reporting the science and technology research trends: report for the ObservatoryNANO.

83. Roco, M. C. (2011). The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. In: Nanotechnology Research Directions for Societal Needs in 2020. *Springer*, pp 1–28.

84. Rodriguez-Lafuente, A., Nerin, C. & Batlle, R. (2010). Active paraffin-based paper packaging for extending the shelf life of cherry tomatoes. *J Agric Food Chem.* 58:6780–6786.

85. Rojas-Graü, M. A., Raybaudi-Massilia, R. M., Soliva-Fortuny, R. C., et al. (2007). Apple puree-alginate edible coating as carrier of antimicrobial agents to prolong shelf-life of fresh-cut apples. *Postharvest Biol Technol.* 45:254–264.

86. Sahu, A., Kasoju, N. & Bora, U. (2008). Fluorescence study of the curcumin – casein micelle complexation and its application as a drug nanocarrier to cancer cells. *Biomacromolecules.* 9:2905–2912.

87. Sandetskaya, N., Allelein, S. & Kuhlmeier, D. (2013). Application of Nanotechnology in Miniaturized Systems and its Use for Advanced Analytics and Diagnostics–an Updated Review. *Recent Pat Food Nutr Agric.* 5:220–238.

88. Santiago, L. G. & Castro, G. R. (2016). Novel technologies for the encapsulation of bioactive food compounds. *Current Opinion in Food Science*. 7, 78-85.

89. Sargent, Jr., JF. (2012). Nanotechnology: A policy primer.

90. Sastry, R. K., Anshul, S. & Rao, N. H. (2013). Nanotechnology in food processing sector-An assessment of emerging trends. *J Food Sci Technol.* 50:831–841.

91. Sayes, C. M. & Warheit, D. B. (2009). Characterization of nanomaterials for toxicity assessment. *Wiley Interdiscip Rev Nanomedicine Nanobiotechnology.* 1:660–670.

92. Sekhon, B. S. (2010). NSA_8677_food-nanotechnology—an-overview. *Nanotechnol Sci Appl.* 3:1–15.

93. Semo, E., Kesselman, E., Danino, D. & Livney, Y. D. (2007). Casein micelle as a natural nano-capsular vehicle for nutraceuticals. *Food Hydrocoll.* 21:936–942.

94. Sharma, V., Shukla, R. K., Saxena, N., et al. (2009). DNA damaging potential of zinc oxide nanoparticles in human epidermal cells. *Toxicol Lett.* 185:211–218. https://doi.org/10.1016/j.toxlet.2009.01.008.

95. Sherman, L. M. (2004). Chasing namocomposites. *Plast Technol.* 50:56–61.

96. Shi, L.-E., Li, Z.-H., Zheng, W., et al. (2014). Synthesis, antibacterial activity, antibacterial mechanism and food applications of ZnO nanoparticles: a review. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 31:173–86. https://doi.org/10.1080/19440049.2013.865147.

97. Shukla, S., Lee, G., Song, X., Park, S. & Kim, M. (2016). Immunoliposome-based immunomagnetic concentration and separation assay for rapid detection of Cronobacter sakazakii. *Biosensors and Bioelectronics*. 77, 986-994.

98. Siegrist, M., Cousin, M.-E., Kastenholz, H. & Wiek, A. (2007). Public acceptance of nanotechnology foods and food packaging: The influence of affect and trust. *Appetite.* 49:459–466.

99. Silvestre, C., Duraccio, D. & Cimmino, S. (2011). Food packaging based on polymer nanomaterials. *Prog Polym Sci.* 36:1766–1782.

100. Singh, T., Shukla, S., Kumar, P., Wahla, V., Bajpai, V. K. & Rather, I. A. (2017). Application of nanotechnology in food science: perception and overview. *Frontiers in microbiology*. 8, 1501.

101. Sonkaria, S., Ahn, S.-H. & Khare, V. (2012). Nanotechnology and its impact on food and nutrition: a review. *Recent Pat Food Nutr Agric.* 4:8–18.

102. Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R. & Rudzinski, W. E. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. *J Control release.* 70:1–20.

103. Su, X. L. & Li, Y. (2004). Quantum dot biolabeling coupled with immunomagnetic separation for detection of escherichia c oli O157: H7. *Analytical chemistry*. 76(16), 4806-4810.

104. Tiwari, R. & Takhistov, P. (2012). Nanotechnology-enabled delivery systems for food functionalization and fortification. *Nanotechnol Res methods foods Bioprod Wiley-Blackwell.* Oxford 55–101.

105. Teow, Y., Asharani, P. V., Hande, M. P. & Valiyaveettil, S. (2011). Health impact and safety of engineered nanomaterials. *Chemical communications*. 47(25), 7025-7038.

106. Tully, E., Hearty, S., Leonard, P. & O'Kennedy, R. (2006). The development of rapid fluorescence-based immunoassays, using quantum dot-labelled antibodies for the detection of Listeria monocytogenes cell surface proteins. *International journal of biological macromolecules*. 39(1-3), 127-134.

107. Viswanathan, S., Wu, L., Huang, M.-R. & Ho, J. A. (2006). Electrochemical immunosensor for cholera toxin using liposomes and poly (3, 4-ethylenedioxythiophene)-coated carbon nanotubes. *Anal Chem.* 78:1115–1121.

108. Vikesland, P. J. & Wigginton, K. R. (2010). Nanomaterial enabled biosensors for pathogen monitoring-a review. *Environmental science & technology*. 44(10), 3656-3669.

109. Wang, S., Su, R., Nie, S., et al. (2014a). Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals. *J Nutr Biochem.* 25:363–376.

110. Wang, Y., Xue, X. & Yang, H. (2014b). Preparation and characterization of carbon or/and boron-doped titania nano-materials with antibacterial activity. *Ceram Int.* 40:12533–12537. https://doi.org/10.1016/j.ceramint.2014.03.082.

111. Weiss, J., Gibis, M., Schuh, V. & Salminen, H. (2010). Advances in ingredient and processing systems for meat and meat products. *Meat Sci.* 86:196–213.

112. Weiss, J., Takhistov, P. & McClements, D. J. (2006). Functional Materials in Food Nanotechnology. *J Food Sci* 71:R107–R116. https://doi.org/10.1111/j.1750-3841.2006.00195.x.

113. Xue, C., Du, G.-Q., Chen, L.-J., et al. (2014). A carbon nanotube filled polydimethylsiloxane hybrid membrane for enhanced butanol recovery. *Sci Rep*. https://doi.org/10.1038/srep05925.

114. Xue, X., Wang, Y. & Yang, H. (2013). Preparation and characterization of boron-doped titania nano-materials with antibacterial activity. *Appl Surf Sci.* 264:94–99. https://doi.org/10.1016/j.apsusc.2012.09.128.

115. Yavlovich, A., Singh, A., Blumenthal, R. & Puri, A. (2011). A novel class of photo-triggerable liposomes containing DPPC: DC 8, 9 PC as vehicles for delivery of doxorubcin to cells. *Biochim Biophys Acta (BBA)-Biomembranes.* 1808:117–126.

116. Yang, L. & Li, Y. (2006). Quantum dot bioconjugates for simultaneous detection of Escherichia coli O157: H7 and Salmonella Typhimurium. *Analyst*. 131(3), 394-401.

117. Yonzon, C. R., Jeoung, E., Zou, S., et al. (2004). A comparative analysis of localized and propagating surface plasmon resonance sensors: the binding of concanavalin A to a monosaccharide functionalized self-assembled monolayer. *J Am Chem Soc*. 126:12669–12676.

118. Zimet, P. & Livney, Y. D. (2009). Beta-lactoglobulin and its nanocomplexes with pectin as vehicles for $ømega$-3 polyunsaturated fatty acids. *Food Hydrocoll* 23:1120–1126.

119. Zhao, X., Hilliard, L. R., Mechery, S. J., Wang, Y., Bagwe, R. P., Jin, S. & Tan, W. (2004). A rapid bioassay for single bacterial cell quantitation using bioconjugated nanoparticles. *Proceedings of the National Academy of Sciences*. 101(42), 15027-15032.

120. Zhou, L., Lv, S., He, G., He, Q. & Shi, B. I. (2011). EFFECT OF PE/AG2O NANO-PACKAGING ON THE QUALITY OF APPLE SLICES. *Journal of Food Quality*. 34(3), 171-176.

Article

The Spreading Cancer of Counterfeit Drugs

Pharmaceutical Fakery Metastasizes from Lifestyle to Lifesaving Medicines

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Journal of Commercial Biotechnology (2020) 25(3), 20–14. doi: 10.5912/jcb940

INTRODUCTION

Just as the coronavirus mutates to survive and thrive, so to do the purveyors of counterfeit medicines – with their high-speed "host" being the digitization of patient care. The future is now. So, how do we balance moving forward with user-friendly digitization, telemedicine and virtual healthcare delivery while simultaneously recognizing the unintended consequences of the innovative criminal mind? The first step is to recognize there's a problem.

COUNTERFEIT MEDICINES: A MOVEABLE FEAST

Once upon a time, at the beginning of the new millennium, counterfeit medicines in the United States were largely "lifestyle" products such as erectile dysfunction drugs – Viagra being the poster child of the problem.[1] Other categories of fake pills included treatments for depression.[2] The common denominator was patient shame and embarrassment. Ordering from seemingly benign (i.e., "from Canada") websites seemed like a safe and anonymous way to address their conditions without having to visit either a physician, mental health professional or pharmacist. A second category of counterfeit prey were people seeking higher risk drugs (opioids, steroids, etc.) to facilitate a more dangerous lifestyle. The rationale for this second group was easier access to more dangerous (often controlled) substances.[3]

To respond to this emerging threat, the FDA formed a Counterfeit Drug Task Force in July 2003.[4] As a former FDA Associate Commissioner, I was proud to serve as a member of that task force. We received extensive comment from security experts, federal and state law enforcement officials, technology developers, manufacturers, wholesalers, retailers, consumer groups and the general public on a very broad range of ideas for deterring counterfeiters. Those comments reinforced the need for the FDA to take action in multiple areas to create a comprehensive system of modern protections against counterfeit drugs.

At the FDA we discussed those ideas and developed a framework for a 21st-century pharmaceutical supply chain that would be more secure against modern counterfeit threats.

The specific approach to assuring that Americans are protected from counterfeit drugs includes the following eight elements:

(1) Implementation of new technologies to better protect our drug supply.
(2) Adoption of electronic track and trace technology.
(3) Adoption and enforcement of strong, proven anticounterfeiting laws and regulations by individual US states.
(4) Increased criminal penalties to deter counterfeiting and more adequately punish those convicted.
(5) Adopstion of secure business practices by all participants in the drug supply chain.
(6) Development of a system that helps ensure effective reporting of counterfeit drugs to the FDA and which strengthens the agency's rapid response to such reports.
(7) Education of consumers and health professionals about the risks of counterfeit drugs and how to protect against them.

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(8) Collaboration with foreign stakeholders to develop strategies to deter and detect counterfeit drugs globally.

According to that report, "Although the safety and security of the U.S. pharmaceutical supply is high, FDA's investigations show that counterfeiting of legitimate drug products poses a significant and growing problem. A multi-prong anti-counterfeiting strategy is necessary to protect consumers by preventing the introduction of counterfeit drugs, facilitating the introduction of counterfeit drugs, and minimizing the risk and exposure of consumers to counterfeit drugs."[5]

Congress also stepped in with legislation, including the Drug Safety and Accountability Act of 2010 and the FDA Globalization Act.[6]

The FDA adopted a global strategy for assuring the safety of the U.S. supply chain that included creation of an office to oversee import safety, with stepped-up powers to interdict incoming drug shipments into the United States, collaborate with regulatory agencies in other countries and order recalls of unsafe products. The agency also called on manufacturers to improve their own screenings of raw materials produced outside the United States — and began ranking more than 1,000 active drug ingredients to assess their "respective risk of economically motivated adulteration," according to then FDA Commissioner Dr. Margaret Hamburg.[7]

In a 2011 analysis of 8,000 rogue websites, the National Association of Boards of Pharmacy concluded that 96% of them were out of compliance with U.S. pharmacy laws, and 85% didn't require a valid prescription.[8]

The FDA required legal distributors to keep detailed records of the sources of the medications they dispense.[9] But it proved to be a futile undertaking swiftly overtaken by advancing digital technologies and criminal talent. Drug counterfeiters have become so sophisticated, they can produce both drugs and packaging that cannot be differentiated from the real thing without complex, time-consuming and costly analyses. It became quickly obvious that paper "pedigrees" were next to useless – but no new strategies, tactics were forthcoming from the FDA and Congress granted the agency neither additional funding nor enhanced regulatory powers to more robustly fight medicines counterfeiting. In 2004, when the FDA claimed that counterfeit drugs were being used to fund global terrorism,[10] many high-profile elected officials accused the agency of being in the pocket of Big Pharma. Today, these same politicians are strangely silent.

Sixteen years later the problem of counterfeit medicines is only getting worse.

COUNTERFEITS ADVANCE FROM LIFESTYLE TO LIFE SAVING DRUGS

When asked why he robbed banks, the Depression Era folk hero Willie Sutton answered, "Because that's where the money is."[11] That same dynamic explains why drug counterfeiters have changed their focus from lifestyle medicines to life saving/extending treatments – particularly oncology treatments (both oral and biological). It's where the money is. Fakes are almost impossible to identify without a sophisticated knowledge of packaging tools and techniques (see Appendix A). The digitization of healthcare has acted as an accelerant to the increased prevalence of and negative impact of counterfeit medicines.

This new and nefarious sales and marketing strategy may be good for the criminal bottom line – but it's deadly for patients.

The FDA has always battled to, on the one hand, empowering patients while, on the other, protecting the public from incorrect, exaggerated and downright phony health information and products. For the FDA, regulatory enforcement surrounding the proliferation of dietary supplements, cannabis and cannabidiol (CBD) products have, at least to-date, been the battleground.[12] Today the issue is the same – a lack of resources and authority to adequately fight multiple battles simultaneously, but the stakes are higher.

According to a recent FDA statement:

FDA lab tests have confirmed that at least one batch of a counterfeit version of Roche's Altuzan distributed in the United States contains no active ingredient. Even if the identified product were not counterfeit, Altuzan (bevacizumab), an injectable cancer medicine, is not approved by FDA for sale in the United States. The only FDA-approved version of bevacizumab for sale in the United States is called Avastin, marketed by Genentech.[13]

The same problem exists in Canada and Europe. The World Health Organization recently warned cancer patients in North America and Europe about a batch of fake drugs that contain nothing but a common painkiller. The product alert says that counterfeit medicine packaged to look like the cancer drug Iclusig, known generically as ponatinib — a targeted therapy for chronic myeloid and acute lymphoblastic leukemia — simply contains acetaminophen.[14] The fakes, discovered by a Swiss wholesaler, have also been detected in Turkey and Argentina.[15]

A week-long, Interpol-coordinated blitz saw authorities in 116 countries seize 500 tons of fake pharmaceuticals worth an estimated $14.000.000. The haul included anti-inflammatory medication, birth control pills, and counterfeit treatments for HIV, Parkinson's and diabetes.

(Investigators also found more than 110,000 fake medical devices like hearing aids, contact lens and syringes.) The seizures resulted in 859 arrests and the closure of 3,671 weblinks.[16]

Rather than attracting otherwise healthy people looking for a quick and private way to purchase low-cost Viagra (out of their own pockets), today's victims are desperately ill patients looking for a way to afford their medicines in the face of rising and perpetual insurance co-payments.[17] The unintended consequences of Prescription Benefit Manager (PBM) tactics such as co-pay accumulators and maximizers[18] as well as Federal government regulations that preclude the use of many patient assistance programs[19] have left patients with cancer and other life-threatening diseases looking for an alternative route to access. Prescription drug counterfeiters have recognized the opportunity and rushed into the breach.[20] Nature abhors a vacuum.

THE ROLE OF SPECIALTY PHARMACY

What has made this possible and predictable is the rapid rise of "Specialty Pharmacy." Specialty pharmacy refers to distribution channels designed to handle pharmaceutical therapies that are either high cost, high complexity and/or high touch (products that require a much higher degree of personal attention and service). Specialty pharmacy requires a higher degree of complexity in terms of distribution, administration and patient management which drives up the cost of the drugs.[21]

Initially specialty pharmacy providers attached "high-touch services to their overall price tags" arguing that patients who receive specialty pharmaceuticals "need high levels of ancillary and follow-up care to ensure that the drug spend is not wasted on them." In the mid 1990s, there were fewer than 30 specialty drugs on the market, by 2008 that number had increased to 200[22] and by 2018 more than 900 unique pharmacy locations received specialty pharmacy accreditation – a 25% increase from 2017.[23]

Importantly, the pharmaceutical industry, in close collaboration with specialty pharmacy, actively and aggressively drove online service and mail-order delivery. Why is specialty pharmacy relevant to the issue of the evolution of counterfeiting? Opportunity.

Specialty pharmacy creates a powerful "cover story" for criminal counterfeiters. Legitimate insurance companies and Prescription Benefit Managers are delivering legitimate medicines through the US Postal Service creating a false sense of security for patients. Two of the serious unintended consequences of using the US Mail are quality and timing problems (see below). Since patients are regularly receiving their medicines through the mail and experience the legitimate system's lack of precision, patients accept the legitimacy of the process. As a result, patients lower their guard and open the door for all types of pharmaceutical interactions that occur virtually or through mail. This creates a dangerous and brightly lit opportunity for counterfeiters to "impersonate" specialty pharmacy and insert counterfeit medicines, via the US Postal Service, into the medicine chests of desperately ill patients. This is the same pathway of opportunity counterfeiters follow when they place a Canadian flag on their phony websites that promise "FDA-Approved Drugs at Canadian prices." (The issue of drug importation will be addressed later in this report.)

While mailing a prescription may sound routine, many of the patients forced to wait for these services are those with complex or life-threatening conditions such as cancer. Delaying these treatments can have serious repercussions for these patients' health and potentially lessens their outlook.

A report from *the Columbus Dispatch* in 2018 highlighted the problem, finding patients like Elvin Weir who not only had to wait for his prescription to be sent to him, but he was also sent the incorrect medication twice. Prescription Benefit Managers (PBMs) and insurers claim that specialty pharmacies help to manage care and costs, but in Mr. Weir's case, their "care" led to a delay in his treatment and the waste of $20,000 worth of treatments.[24]

Another 2018 report from *the Times-Picayune* in New Orleans highlighted how numerous cancer patients are forced to wait or are outright denied the medication their doctor has prescribed them, forcing them to wait for an appeal. In the instance highlighted, the patient, Connie Raborn, had to wait almost three months before she was able to take her medication.[25]

Such delays aren't the only problems facing patients using a specialty or mail-order pharmacy. Patients have reported receiving medications which were shipped at unsafe temperatures, rendering them ineffective or even dangerous.[26] It is a short step from substandard medicines to counterfeit ones.

THE REGULATORY LIMITATIONS OF PRODUCT SERIALIZATION

Serialization refers to the requirements for application of a unique identification code, a serial number or electronic product code (EPC). Serial numbers can be tracked through its entire supply chain, from production to retail distribution to final dispensation to the patient.[27]

The FDA believes that counterfeiting can be reduced significantly through product serialization. Serialization requires a comprehensive system to track and trace the passage of prescription drugs through the entire supply chain. Serialization can potentially identify every product by a unique serial number in addition to the origin, shelf life and batch number for that product. This could potentially allow the product's lifecycle to be traced from production, through distribution, and finally to the patient.

But serialization is not just about generating unique serial numbers, but also creating and maintaining identification tools that provide visibility and full traceability within the supply chain. It requires collaborative action from partners throughout the supply chain for accurate recording, tracking and managing of data as the product moves from manufacturer, to distributor, to the dispensing point. It's expensive and complex proposition. That complexity creates a multitude of opportunities for criminal counterfeiters motivated by huge profits on placing their fake products into the medicine chests of American patients.

THE DRUG QUALITY AND SECURITY ACT

As part of a long-term strategy, the United States has been trying to move to implementing technology and systems that would discourage the introduction and distribution of counterfeit drugs. In November 2013, President Obama signed into law the Drug Quality and Security Act (DQSA) (H.R. 3204).[28] Implicit within the DSQA is the Drug Supply Chain Security Act (DSCSA) which outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the U.S. This law established requirements to facilitate the tracing of prescription drug products through the pharmaceutical supply distribution chain (H.R.3204 – Drug Quality and Security Act, 2018).[29]

Full execution of Title II of the DQSA[30] dictates that data will be exchanged across a very complex and diverse set of supply chain partners: in-house packaging facilities, packaging facilities of contract development and manufacturing organizations (CDMOs), third-party logistics providers (3PLs), repackagers, wholesalers, and dispensers. However, the aggregation of serialized data is not a requirement of the DQSA.

Data must have high integrity and be free of corruption for effective use by members of the pharmaceutical supply chain, and data must be protected from hackers and other cyber criminals. Serialization is, of course, meant to protect and validate the identity of a product throughout the supply chain. Therefore, it does not take much of a leap of imagination to envision how cyber-counterfeiters benefit by manipulating the identity of high-value products – at the expense of patients' seeking lower costs due to ever-increasing co-payments driven by the costs of specialty pharmacy and the desire of PBMs to further increase their bottom-line profits.[31]

Theoretically, by the end of 2023 (the deadline for full track-and-trace implementation) an enormous amount of data will be generated at operational speeds, correctly assigned to a given product, stored, and transmitted to all appropriate supply chain partners. That data will then need to flow seamlessly between clients and their Contract Development and Manufacturing Organization (CDMO) or Contract Packaging Organization (CPO).[32] Theoretically. However, as the biopharmaceutical industry, its supply chain partners, PBMs (and their specialty pharmacy divisions), regulators and lawmakers continue to discuss, debate and finesse serialization in all its forms, criminal counterfeiters are exploiting the holes in the system, enhancing their false profits through savvy exploitation of technology and regulatory gaps – at the expense of patient health.

HHS OFFICE OF INSPECTOR GENERAL REPORT: THE DRUG SUPPLY CHAIN SECURITY ACT (DSCSA)

In February 2020, the US Department of Health and Human Services Office of Inspector General issued a report[33] that stated:

Drug diversion, counterfeiting, and the importation of unapproved drugs may result in potentially dangerous drugs entering the drug supply chain, posing a threat to public health and safety. To enhance the security of this supply chain, the DSCSA requires trading partners in the drug supply chain to create a record of each drug product transaction. FDA can use these records to investigate and identify potentially harmful drug products, prevent further distribution, and facilitate efficient recalls.

According to the report, ownership of 37 of 44 selected drug products could be traced through the supply chain using drug product tracing information that the Drug Supply Chain Security Act (DSCSA) requires. Seven selected drug products could not be completely traced to manufacturers. Typically, this was because tracing documents exchanged between the wholesale distributor and manufacturer were missing or had mismatched tracing information.

In one instance, a wholesale distributor refused to provide tracing documents. When tracing information is missing or mismatched, a complete tracing record for a drug product may not always be available to support investigations of suspect or illegitimate drug products in the supply chain, which could delay investigators. Indeed, staff at the Food and Drug Administration (FDA) reported that accurate tracing information is critical to identifying a drug product quickly in the event of a recall or when removing an illegitimate drug product from the supply chain.

Additionally, for 21 of 44 selected drug products, the Inspector General found that—unlike with their ownership—they could not trace their physical movement through the supply chain using tracing information. Nor could the OIG identify the shipping locations of trading partners (e.g., manufacturers, wholesale distributors, and dispensers) or third-party logistics providers that shipped or stored the drugs on behalf of the trading partners. Although the DSCSA does not require this information, should FDA not have access to this information in case of a drug safety emergency, FDA and other investigators would need to request additional documents, which could delay investigations and hamper FDA's ability to identify sources of potentially harmful drugs in a timely manner.

The OIG report recommends that FDA follow up with the wholesale distributor that did not provide tracing information. The OIG also recommends that FDA offer educational outreach to trading partners about required drug product tracing information and data standardization guidelines. Lastly, the OIG recommends that FDA seek legislative authority to require information about a drug product's complete physical path through the supply chain on tracing information. FDA concurred with all of the OIG report recommendations.

BAD POLICY IDEAS HAVE NEGATIVE REAL-WORLD CONSEQUENCES

We live in a hyper-politicized environment often driven by simplistic, soundbite solutions to complex problems – such as the cost of medicines. In the case of counterfeit medicines, they can actually exacerbate the problem. A good example of this issue is Drug Importation (aka: "Drugs from Canada").

The concept sounds easy and logical but, as HL Mencken said, "For every complex problem there is an answer that is clear, simple, and wrong." All importation schemes offer lower cost medicines with no additional risk. The facts, however, point to neither savings – nor safety.

During a weeklong anti-counterfeiting operation Canadian officials inspected nearly 3,600 packages — and found that 87 percent contained counterfeit or unlicensed health products.[34] A striking number of "Canadian" drugs aren't actually from Canada. Canadian internet pharmacies regularly import drugs from less developed[35] and less regulated countries, like Turkey. Then they slap on their own labels and ship them elsewhere.[36] One FDA operation found 85 percent of "Canadian" drugs originated in 27 different countries and more than a third of those drugs were potentially counterfeit.[37]

Such concerns explain why Illinois ditched its importation program, I-SaveRX, in 2009 after failing to adequately inspect foreign pharmacies. According to a state audit, "40 percent of the required inspections of the foreign entities claiming to be pharmacies were never completed, putting patients at risk" and patients were left with "no regulator to protect them."[38]

Canadian regulators have warned Americans that importation could be risky. One official at Health Canada, the government agency which oversees that nation's pharmaceutical supply[39], said the regulator "does not assure that products being sold to U.S. citizens are safe, effective and of high quality and does not intend to do so in the future."[40] Safety cannot be ignored because it is inconvenient.

Senior U.S. officials have issued similar warnings. Over the past 18 years, in both Democrat and Republican administrations, every FDA commissioner and secretary of Health and Human Services has failed to certify that importation is safe.[41]

However, recently, The Department of Health and Human Services (HHS) recently floated a proposal, dubbed the Safe Importation Plan, to allow Americans to use Canada as their personal pharmacy.[42] In Canada, the government dictates the market through price controls, but any drug importation scheme should give Americans pause.[43]

The so-called Safe Importation Action Plan offers two paths forward for drug importation. First, states, wholesalers or pharmacists could submit plans for demonstration projects for HHS to review outlining how they would import Health Canada-approved drugs, Second, manufacturers could import versions of existing FDA-approved drugs into the United States.

The plan sounds reasonable enough, but it's missing one key variable — the Canadian government. Neither the Trump Administration nor any state that's been pondering drug importation has ever consulted the Canadian government.[44] Had they done so; they'd see that our neighbors to the north have some serious concerns with the proposal.

Access to high-quality medicines is a crucial issue, but drug importation is not the answer. The Trump

Administration's drug importation plan would create more problems than it would solve by jeopardizing Canada's drug supply and exposing Americans to deadly counterfeits.

THE CDC AND THE "EPIDEMIOLOGY OF COUNTERFEITING"

Through literature review, interviews, surveillance and research, discover new data about counterfeiting as a risk to public health. With a lack of information on the public safety impact of on the most at-risk populations (economically disadvantaged, elderly, under-insured), the Centers for Disease Control and Prevention (CDC) should develop and field a study on the adverse health effects of counterfeit medicines. The scope of such a project should include:

- Raising awareness of counterfeit medicines as a public health issue within CDC and among its partners.
- In-depth interviews to determine which CDC programs and partners use prescription drugs in prevention, intervention, treatment and surveillance programs, identify baseline awareness of counterfeit medicine within the same groups.
- A literature review to determine if there is existing evidence of counterfeit medicines in the peer-reviewed literature, assess the current landscape (and associated consumer harms) and identify gaps and areas for future research.
- Collect data and determine commonalities of counterfeit-related injuries, disease, identify determinants and identify further areas for prevention.
- Develop a report to summarize key findings and recommendations, including potential subject matter experts, opportunities for further collaboration, and development of a framework for additional phases of research.

COUNTERFEITS AND COVID: PROBLEM AND OPPORTUNITY

Not surprisingly, the COVID-19 pandemic has increased the public's exposure to counterfeit medical products.

According to the FDA:

The FDA advises consumers to be cautious of websites and stores selling products that claim to prevent, treat or cure COVID-19. There are no FDA-approved products to prevent COVID-19. Products marketed for veterinary use, or "for research use only," or otherwise not for human consumption, have not been evaluated for safety and should never be used by humans. For example, the FDA is aware of people trying to prevent COVID-19 by taking a product called chloroquine phosphate, which is sold to treat parasites in aquarium fish. Products for veterinary use or for "research use only" may have adverse effects, including serious illness and death, when taken by people. Don't take any form of chloroquine unless it has been prescribed for you by your health care provider and obtained from legitimate sources.

The sale of fraudulent COVID-19 products is a threat to the public health. If you are concerned about the spread of COVID-19, talk to your health care provider and follow the advice of FDA's federal partners.[45]

The FDA recognizes the threat of criminals preying on the COVID-19 fears of the American public. The agency acted quickly and aggressively issue warnings and ramp up enforcement. Perhaps, in a post-COVID environment, the FDA will pursue the threat of counterfeit medicines in a more proactive, manner.

REINFORCING THE STRONGEST LINK IN THE CHAIN

The war against counterfeiting requires robust leadership, new strategies and tactics. The Center for Medicine in the Public Interest believes the FDA is the most appropriate federal authority to lead our nation's anti-counterfeiting efforts. And the first order of business is to create a taskforce that includes other entities from the US Department of Health and Human Services (National Institutes of Health, Centers for Disease Control), other cabinet-level departments (Justice, Commerce, Homeland Security, the White House, etc.), state-level authorities, professional and patient organizations. You can't win a war without a war room. And you cannot fight battles without precise coordination of resources and effort.

The most potent tool in the struggle against counterfeiting is product integrity. Quality is hard to maintain, and counterfeiters don't care about it. That is their Achilles Heel. Advancing and protecting quality is the most powerful weapon in the fight counterfeit medicines.

Comprehensive product quality and supply-chain security requires a multi-layer approach that includes prevention, detection, and response strategies and

actions. The battle against counterfeit medicines requires a comprehensive resource that addresses areas of vulnerability in the medical product supply chain and contains recommended best practices and tools to prevent and detect substandard and falsified medical products before they reach consumers. Such a resource must also provide tools to efficiently and effectively respond to incidents involving substandard and falsified medical products.

Consider the FDA's Supply Chain Security Tool Kit announced earlier this year. The toolkit contains training materials intended to educate regulators, industry, health care professionals, and others on a particular part of the supply chain in 10 categories:

- good manufacturing practices;
- good distribution practices;
- good import/export practices;
- clinical/retail pharmacy practices;
- product security;
- detection technology;
- internet sales;
- track and trace systems;
- surveillance and monitoring; and
- single points of contact.

According to the FDA, "The toolkit will be used by industry stakeholders and regulators from around the globe to adopt best practices, for training purposes, and to strengthen laws and regulations to protect consumers from unsafe and substandard drug products. APEC Training Centers of Excellence for Regulatory Science (CoE) will be established to further training and use of the toolkit."[46]

This is an important and timely effort and should be supported with more than just rhetoric. As we enter into PDUFA reauthorization discussions[47], support of this initiative should be a priority.

But the FDA can do more. As the strongest link in the chain, the FDA must also be at the forefront of stronger criminal prosecution (in close collaboration with the Department of Justice), enhanced enforcement of dietary supplement health claims (together with the FCC and the Department of Commerce), targeted education efforts to oncology professionals (physicians, nurses, pharmacists), patients, caregivers and payers (alongside the National Cancer Institute).

It is also important that the FDA not undermine its own efforts by "going soft" on ill-considered policies that support the importation of foreign prescription medicines (see above section, "Bad Policy Ideas Have Negative Real-World Consequences"). Just as the embrace of specialty pharmacy has created an opportunity for criminal counterfeiting, so too does the patina of FDA "approval" of the importation concept. It is essential that the FDA actively avoid allowing its own words to provide cover for those who would harm the public health for their own profit. Friendly fire is often the most costly.

Source: http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChainToolkit_170317.pdf

MOVING FORWARD: 10 STEPS TO VICTORY

1. **Increase awareness of counterfeit threat**, particularly associated with life-extending/saving medicines, among patients and health care providers
2. **Differentiate target audiences** – Demand reduction for Patients/HCPs to prevent inadvertent purchase of suspect product. Partner with law enforcement to address willful violators.
3. **Demand reduction must be measurable** (per HHS/OIG report).
4. **Create personal serialization validation tools** to enable patient participation.
5. **Conduct a CDC "Epidemiology of Counterfeit Medicines" study** – how many patients actually die or are seriously harmed by counterfeit oncology medicines? Who are they?[48]
6. **Enhance productive industry/government intelligence/information exchange**.
7. **Better use of existing government resources and authorities** for more effective protection of patients/citizens.
8. **Enhance Industry/Government collaboration on demand reduction**.
9. **Eliminate use of the internet as a commercial platform** by effectively educating and partnering with recalcitrant ISPs.[49]

10. **Increase awareness programs for the general population** of the problem and of programs that reduce co-payment costs.

CONCLUDING THOUGHTS

The unfortunate reality is that urgent public health issues (such as COVID-19 and the danger of counterfeit drugs) that should be strictly non-political are being seen, first-and-foremost, as opportunities by special interest groups and many of our elected representatives to "score points." The media, alas, swarms to cover these blood feuds, almost entirely obfuscating the scope and severity of the problem. When it comes to counterfeit drugs, the alarm bells sounded by the biopharmaceutical industry are too often waved off as an attempt to distract attention from "the high cost of drugs." While such exhortations are tactically successful in attracting transient media coverage, it does a tremendous disservice to the public by masking the urgency of the problem.

As Scientific American reports, "In a fiercely competitive business. For those who like pharma scandals, their paper offers detailed examples, *a la* "The Constant Gardener," of pharmaceutical companies trying to bury their problems quietly."[50]

During my tenure on the FDA's Counterfeit Drug Task Force, I witnessed first-hand the evolution of thinking within the biopharmaceutical industry. Initially, as suggested by Scientific American article, industry's response was to address the problem but say nothing publicly for fear of counterfeit drugs tainting their own reputation. When pressed by the FDA Task Force to take a more public leadership position, industry swiftly stepped up to the plate, partnering with the FDA and other government agencies (on both the federal and state levels) to more publicly and aggressively address the problems associated with mitigating and preventing the growth of counterfeit drugs in the United States.

Per Scientific American, "Pharma shows increased recognition that openness to the problem and notification of the public is not only the appropriate response but will likely reduce their liability and is otherwise in their self-interest.[51]

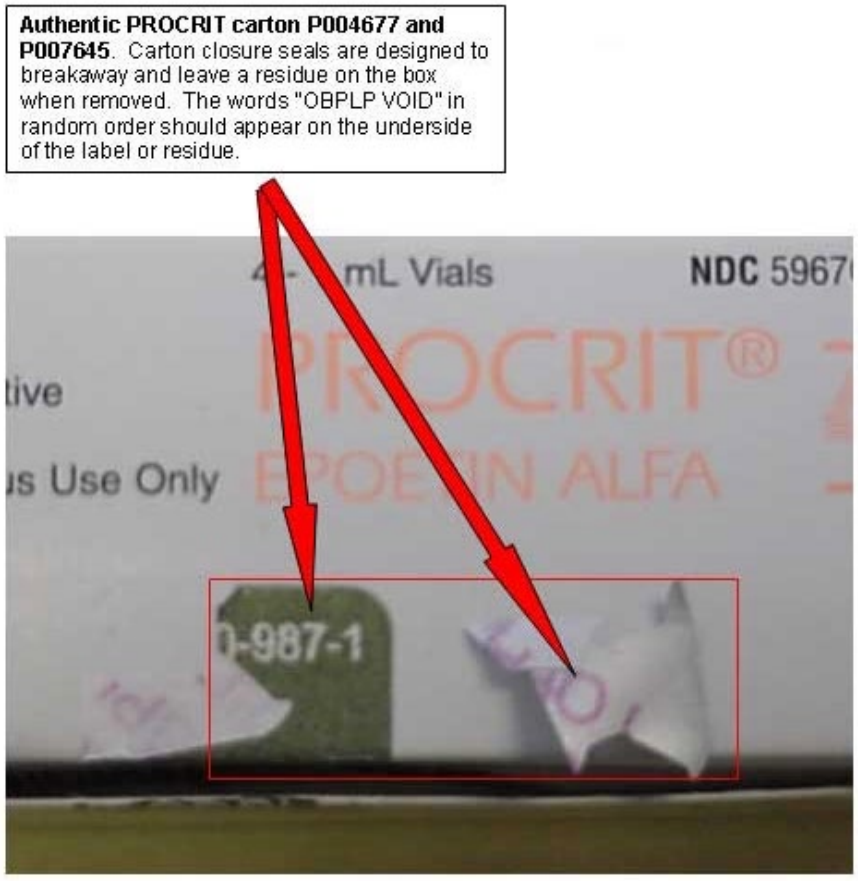
According to the FDA Task Force's initial report, "Based on what it has heard to date, the Task Force believes that the most constructive approach to addressing the problem of counterfeit drugs lies in identifying vulnerabilities in the drug distribution system and addressing those vulnerabilities with a multi-pronged approach."

It isn't the "cost of drugs" drives desperately ill patients into the arms of counterfeiters, it is, in the majority, the cost of patient co-pays. Larger and larger co-pays and out-of-pocket costs magnify the problem by creating a criminal opportunity. Better, more targeted and aggressive regulation together with more regular and robust law enforcement is key – but when patients cannot afford their co-pay for life-saving medicines the incentive for quick fix solutions via a website that promises to provide the genuine article is almost irresistible.

As the old Yiddish proverb reminds us, "Sometimes a bargain is too expensive." And sometimes its deadly. The time is now. Action must be taken. Attention must be paid.

APPENDIX A

Examples of Counterfeit Biologics Packaging

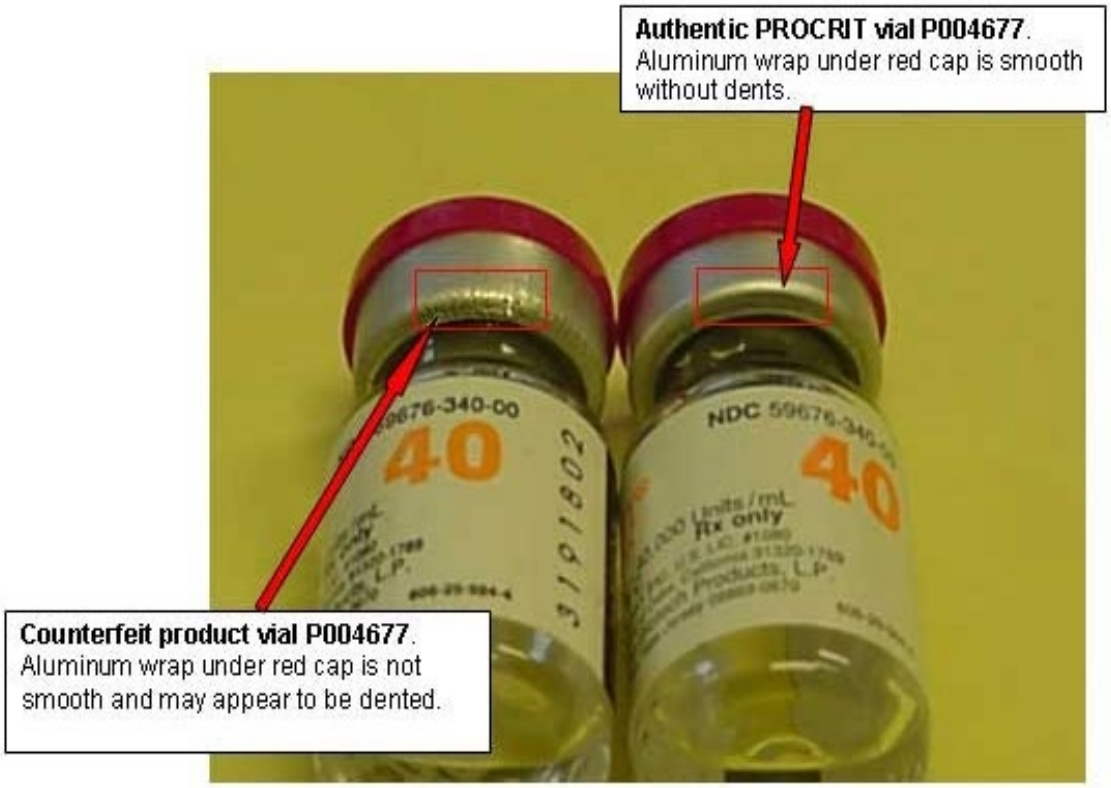


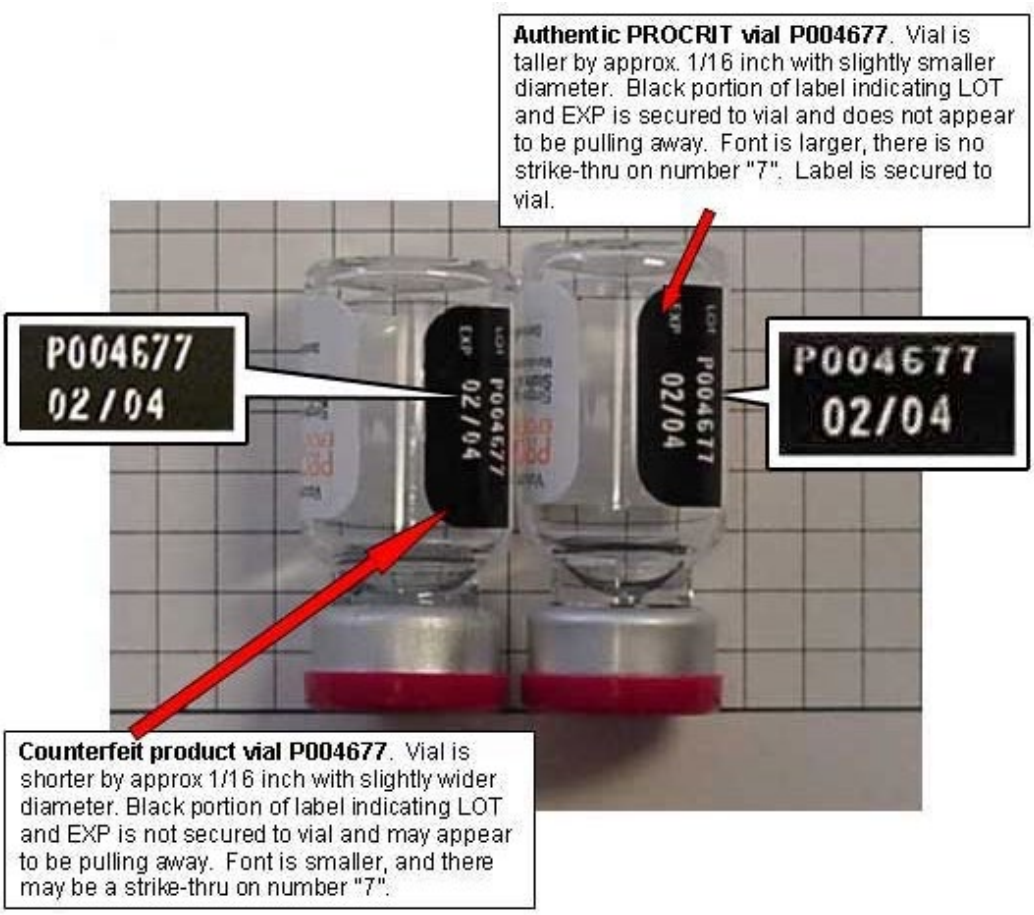
AMGEN

Blue Amgen logo is seen when held at waist height.

COUNTERFEIT

Blue Amgen logo is seen when held at waist height.


Authentic PROCRIT vial P004677.
Aluminum wrap under red cap is smooth without dents.
Counterfeit product vial P004677.
Aluminum wrap under red cap is not smooth and may appear to be dented.
40
40
Rx only


Authentic PROCRIT vial P004677. Vial is taller by approx. 1/16 inch with slightly smaller diameter. Black portion of label indicating LOT and EXP is secured to vial and does not appear to be pulling away. Font is larger, there is no strike-thru on number "7". Label is secured to vial.
P004677
02/04
P004677
02/04
Counterfeit product vial P004677. Vial is shorter by approx 1/16 inch with slightly wider diameter. Black portion of label indicating LOT and EXP is not secured to vial and may appear to be pulling away. Font is smaller, and there may be a strike-thru on number "7".

ABOUT THE AUTHOR

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His comments and commentaries on health care policy issues regularly appear in The New York Times, The Washington Post, The Wall Street Journal, the Lancet, Nature Biotechnology, among others. He is the editor of **Coincidence or Crisis**, a discussion of global prescription medicine counterfeiting, **Physician Disempowerment: A Transatlantic Malaise** and **Commonsense Healthcare Policy for Commonsense Americans.** He is a Visiting Professor at the University of Paris, Descartes Medical School, a Visiting Lecturer at the École Supérieure des Sciences Économiques et Commerciales (Paris and Singapore), and has served as an adjunct professor at Indiana University's School of Public and Environmental Affairs and Butler University.

ENDNOTES

1. https://www.pharmaceutical-technology.com/features/featuretackling-counterfeit-viagra-4970635/ Last accessed June 4, 2020
2. https://www.cnbc.com/2018/08/02/antianxiety-drugs-fuel-the-next-deadly-drug-crisis-in-us.html Last accessed June 4, 2020
3. https://www.dea.gov/press-releases/2019/11/04/dea-issues-warning-over-counterfeit-prescription-pills-mexico-0 Last accessed June 4, 2020
4. https://www.medscape.com/viewarticle/460566 Last accessed June 4, 2020
5. https://www.fda.gov/media/77086/download
6. https://www.congress.gov/bill/111th-congress/senate-bill/3690 Last accessed June 4, 2020
7. https://www.c-span.org/video/?295894-4/margaret-hamburg-remarks-counterfeit-perscription-drugs Last accessed June 4, 2020
8. https://nabp.pharmacy/newsroom/news/nabp-issues-rogue-online-pharmacy-public-health-alert/ Last accessed June 4, 2020
9. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1305&showFR=1&subpartNode=21:9.0.1.1.6.3 Last accessed June 4, 2020
10. https://scholarlycommons.law.case.edu/cgi/viewcontent.cgi?referer=&httpsredir=1&article=1022&context=jil Last accessed June 4, 2020
11. https://en.wikipedia.org/wiki/Sutton%27s_law Last accessed June 4, 2020
12. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary Last accessed June 4, 2020
13. https://www.fda.gov/drugs/counterfeit-medicine/health-care-provider-alert-another-counterfeit-cancer-medicine-found-united-states Last accessed June 4, 2020
14. https://cmlnetwork.ca/counterfeit-iclusig-ponatinib/ Last accessed June 4, 2020
15. https://www.theguardian.com/society/2019/feb/12/fake-cancer-drug-made-from-paracetamol-world-health-organization Last accessed June 4, 2020
16. https://www.interpol.int/News-Events/2018/N2018-123 sLast accessed June 4, 2020
17. https://www.healthcarepackaging.com/markets/pharmaceutical/news/13294907/counterfeiters-move-from-lifestyle-drugs-to-lifesaving-drugs Last accessed June 4, 2020
18. https://cmpi.org/in-the-news/health-care-chutzpah-vs-health-plan-literacy Last accessed June 4, 2020
19. https://www.taftlaw.com/news-events/law-bulletins/hhs-oig-approves-narrowly-tailored-patient-assistance-program Last accessed June 4, 2020
20. https://www.cbc.ca/news/thenational/national-today-newsletter-counterfeit-drugs-medicine-1.5014784 Last accessed June 4, 2020
21. https://en.wikipedia.org/wiki/Specialty_pharmacy Last accessed June 4, 2020
22. https://en.wikipedia.org/wiki/Specialty_drugs_in_the_United_States Last accessed June 4, 2020
23. https://www.drugchannels.net/2019/04/the-specialty-pharmacy-boom-our.html Last accessed June 4, 2020
24. https://www.dispatch.com/news/20180603/mail-order-pharmacy-system-delays-meds-for-some-patients Last accessed June 25, 2020
25. https://www.nola.com/entertainment_life/health_fitness/article_6ad30efb-0cca-5900-90ed-62badf5ac35b.html Last accessed June 25, 2020
26. https://www.spokesman.com/stories/2018/dec/05/peoples-pharmacy-will-breast-cancer-drug-work-if-s/ Last accessed June 25, 2020
27. https://www.aniglobalsource.com/blog/serialization-what-it-means-for-pharmaceutical-manufacturing Last accessed June 4, 2020

28. https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa Last accessed June 4, 2020
29. Ibid Last accessed June 4, 2020
30. https://www.fda.gov/drugs/drug-supply-chain-security-act-dscsa/title-ii-drug-quality-and-security-act Last accessed June 4, 2020
31. https://www.newsweek.com/big-pharma-villain-pbm-569980 Last accessed June 4, 2020
32. https://www.pewtrusts.org/-/media/assets/2014/04/29/boozallenhamiltonreport.pdf Last accessed June 4, 2020
33. https://oig.hhs.gov/oei/reports/oei-05-17-00460.pdf Last accessed June 4, 2020
34. https://www.safemedicines.org/2019/01/raid-in-british-columbia-canada-turns-up-a-pill-press-and-over-100-different-pill-dyes.html Last accessed June 4, 2020
35. https://www.safemedicines.org/2015/10/5-secrets-canadian-pharmacies-dont-want-you-to-know.html Last accessed June 4, 2020
36. https://www.nytimes.com/2004/08/11/us/vermont-will-sue-us-for-the-right-to-import-drugs.html Last accessed June 4, 2020
37. http://www.safemedicines.org/wp-content/uploads/FDA-Operation-Reveals-Many-Drugs-Promoted-as-_Canadian_-Products-Really-Originate-From-Other-Countries-captured-January-2017.pdf Last accessed June 4, 2020
38. https://www.safemedicines.org/2015/11/illinois-and-isaverx.html Last accessed June 4, 2020
39. https://www.canada.ca/en/health-canada/corporate/about-health-canada.html Last accessed June 4, 2020
40. http://www.safemedicines.org/wp-content/uploads/2018/03/HHS-Report1220.pdf Last accessed June 4, 2020
41. https://www.safemedicines.org/2018/07/who-opposes-drug-importation-every-head-of-the-fda-and-hhs-since-2000.html Last accessed June 4, 2020
42. https://www.hhs.gov/about/news/2019/07/31/hhs-new-action-plan-foundation-safe-importation-certain-prescription-drugs.html Last accessed June 4, 2020
43. https://www.healthaffairs.org/doi/full/10.1377/hlthaff.20.3.92 Last accessed June 4, 2020
44. Author's conversations with Canadian government officials
45. https://www.fda.gov/consumers/consumer-updates/beware-fraudulent-coronavirus-tests-vaccines-and-treatments Last accessed June 4, 2020
46. https://www.fda.gov/drugs/drug-supply-chain-integrity/fda-leads-effort-create-supply-chain-security-toolkit-medical-products Last accessed June 25, 2020
47. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022 Last accessed June 25, 2020
48. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164397/ Last accessed June 4, 2020
49. https://www.fraserinstitute.org/sites/default/files/pharmaceutical-counterfeiting-endangering-public-health-society-and-the-economy.pdf Last accessed June 4, 2020
50. https://blogs.scientificamerican.com/molecules-to-medicine/counterfeit-drugs-a-deadly-problem/ Last accessed June 4, 2020
51. Ibid Last accessed June 4, 2020

Article

Could COVID-19 Cause 'Biopharming' to Bloom?

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ABSTRACT

At an accelerated rate in response to the COVID-19 pandemic, academic and corporate scientists are using genetic engineering techniques to reprogram plants to produce significant concentrations of high-value pharmaceuticals. The concept is not new. Many common medicines, such as certain opiates, the laxative Metamucil, and the anti-cancer drug Taxol, are all purified from plants, and efficacy has been shown for some herbals in Traditional Chinese Medicine. There is great potential for cost-cutting in the process: The energy for product synthesis comes from the sun, and the primary raw materials are water and carbon dioxide. In addition, biopharming offers tremendous flexibility and economy when adjustments in production are necessary. The need for inexpensive, flexible production techniques for COVID-19 therapeutics and vaccines could be a potent stimulus to biopharming research and development.

Journal of Commercial Biotechnology (2020) 25(3), 34–36. doi: 10.5912/jcb941

The COVID-19 pandemic has spurred profound changes in the scientific research community worldwide. Laboratories have reoriented their research to focus on various aspects of this scourge, and thousands of articles have already appeared on preprint servers and in journals. As scientific researchers race to find solutions, the production of high-value pharmaceuticals in plants, or "biopharming," a technology that has teetered on the brink of recognition for many years, is mushrooming. The pandemic could be an opportunity to prove its worth.

Academics and biotech companies are using genetic engineering techniques to reprogram plants — which have included corn, potatoes, rice, and bananas, among others (discussed below) — to produce significant concentrations of pharmaceuticals, including vaccines. The concept is not new. Many common medicines, such as morphine, codeine, the laxative Metamucil, and the anti-cancer drug Taxol, are all purified from plants. There are also a few examples of Chinese herbal treatments that have proved effective in randomized controlled clinical trials. One notable product that has emerged from Traditional Chinese Medicine, or TCM, is artemisinin. First isolated by Youyou Tu at the China Academy of Traditional Chinese Medicine in Beijing, the molecule is now a powerful treatment for malaria and led to Tu being awarded the Nobel Prize in Physiology or Medicine in 2015 (Callaway, and Cyranoski, 2015).

But biopharming's great promise lies in using genetic engineering techniques to make old plants do radically new things.

There is also great potential for cost-cutting in the process: The energy for product synthesis comes from the sun, and the primary raw materials are water and carbon dioxide. In addition, biopharming offers tremendous flexibility and economy when adjustments in production are necessary. Doubling the acreage of a crop requires far less capital than doubling the capacity of a bricks-and-mortar factory, making biopharmed drugs potentially much less expensive to produce than those made in conventional ways. As little as 2,000 acres can provide the substrate for a year's supply of some products. Grain from a biopharmed crop can be stored safely for long periods with no loss of activity. The quality of the final drug can meet the same standards as current fermentation technology using microorganisms.

In addition, biopharmed vaccines are inexpensive to produce, easy to upscale, and often do not require

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refrigeration, needles or trained medical personnel, thus making them attractive for use in developing countries. Many research studies and clinical trials have shown that plant-made vaccines elicit a robust immune response in animals and humans and are safe and efficacious (Paul and Ma, 2011). Examples of plant-made vaccines and therapeutics produced by molecular pharming include vaccines to combat cholera, Dengue fever virus and Hepatitis B virus; and monoclonal antibodies to HIV and Ebola virus.

Although such plant biologics have largely focused on the diseases of the poor in developing countries, they have found other niches as well. For example, several plant-made vaccines to combat pandemic influenza are currently completing clinical trials and will soon be on the market, and plant-based immunotherapies to treat a variety of cancers are in development (Mardanova and Ravin, 2018). A plant-based therapeutic to provide the enzyme glucocerebrosidase in Gaucher Disease patients has also found a reliable market and is currently commercially available (Grabowski et al., 2014).

Several biopharming companies and academic research labs have taken up the challenge to combat COVID-19. Medicago, a Canadian biopharmaceutical company, successfully developed a virus-like particle (VLP) of the coronavirus only 20 days after obtaining the SARS-CoV-2 genetic sequence. Instead of using egg-based methods to produce a vaccine, this technology inserts a genetic sequence that encodes the spike protein of COVID-19 into Agrobacterium, a common soil bacterium that is taken up by plants (Krenek et a., 2015). The resulting plants produce a VLP that is composed of plant lipid membrane and COVID-19 spike protein, and which acts as the vaccine. The VLPs are similar in size and shape to actual coronavirus but lack viral or plant nucleic acid and are thus noninfectious.

Previously, Medicago made VLPs that contain influenza virus hemagglutinin and demonstrated their safety and efficacy in animal models as well as in human clinical trials (Pillet et al., 2019). The cost of producing a plant-made vaccine based on VLPs is a small fraction compared to its conventional counterparts.

Also in Canada, the University of Western Ontario and Suncor are developing serological test kits for COVID-19 using algae as a production factory to make the viral spike proteins (Mackay, 2020). Algae has long been considered a potential platform for generating pharmaceutical proteins as well as industrial proteins such as cellulases (Specht and Mayfield, 2018). Algae is a superior bio-factory alternative because it is easy to grow at scale and can be readily modified to produce the viral proteins.

British American Tobacco, through its biotech subsidiary in the US, Kentucky BioProcessing (KBP), is developing a potential vaccine for COVID-19 that is currently undergoing pre-clinical testing (Gretler, 2020). Experts at KBP cloned a part of the genetic sequence of SARS-CoV-2, which they used to develop a potential antigen that was inserted into *Nicotiana benthamiana* plants for production. The vaccine elicited a positive immune response in preclinical testing and is expected soon to begin Phase 1-2 clinical trials (Clinicaltrials.gov, 2020). BAT could manufacture as much as 1-3 million doses of COVID-19 vaccine per week. (They were able to make 10 million doses of flu vaccine and of an Ebola vaccine in a month, using the same plant-based approach.)

South African company Cape Bio Pharms (CBP) is also responding to the COVID-19 pandemic with the production of reagents in plants that could be used in diagnostic kits (Nogrady, 2020). CBP is producing SARS-CoV-2 Spike S1 reagents consisting of various regions of the glycoprotein attached to various fusion proteins. The company is also collaborating with antibody manufacturers to produce antibodies against these proteins.

Another example of a biopharming solution to COVID-19 is being developed in Professor Nicole Steinmetz's lab at the University of California, San Diego, using Cowpea mosaic virus VLPs with epitopes from COVID-19 displayed on their icosahedral surfaces (Wang et al., 2019). The VLPs harboring these COVID-19 epitopes can be administered in the form of a microneedle technology, which delivers drugs painlessly through the skin, eliciting an immune response to SARS-CoV-2 (Lopez-Ramirez et al., 2020).

A collaboration between research groups in Toronto, Canada, is working on a novel way to both prevent and treat COVID-19 using an antiviral protein that blocks virus replication (Jain, 2020). When loaded onto a plant virus nanoparticle, the protein can enter cells and block virus infection. It is possible that this biopharmed antiviral protein can be loaded into an inhaler and administered to the lungs of infected and uninfected patients. Similarly, a synthetic, plant-made antibody has been designed to prevent virus infection and block person-to-person transmission. It can be produced easily in plants engineered to synthesize antibodies that are as "humanized" as possible, reducing the likelihood that patients' immune system will reject them as "foreign."

In our pandemic world, collaborations and markets have begun to mix and merge in unprecedented ways. While more than a hundred COVID-19 vaccine candidates are moving forward at various stages of development, it is difficult to predict which will ultimately be successful. The rapid and easy scalability of plants, combined with the power and versatility of molecular genetic engineering techniques, could offer the kind of rapid response and flexibility that is needed.

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REFERENCES

1. Callaway, E. & Cyranoski, D. Anti-parasite drugs sweep Nobel prize in medicine 2015. *Nature News*. October 5, 2015.
2. Paul, M. & Ma, J. K.-C. (2011). Plant-made pharmaceuticals: Leading products and production platforms. *Biotechnology and Applied Biochemistry*. 58, 58-67. https://doi.org/10.1002/bab.6.
3. Mardanova, E. S. & Ravin, N. V. (2018). Plant-produced Recombinant Influenza A Vaccines Based on the M2e Peptide. *Curr Pharm Des*. 24(12), 1317-1324. https://doi.org/10.2174/1381612824666180309125344.
4. Grabowski, G. A., Golembo, M. & Shaaltiel, Y. (2014). Taliglucerase alfa: an enzyme replacement therapy using plant cell expression technology. *Mol Genet Metab*. 112(1), 1-8. https://doi.org/10.1016/j.ymgme.2014.02.011.
5. Krenek, P., Samajova, O., Luptovciak, I., Doskocilova, A., Komis, G. & Samaj, J. (2015). Transient plant transformation mediated by Agrobacterium tumefaciens: Principles, methods and applications. *Biotechnol Adv*. 33(6 Pt 2),1024-1042. https://doi.org/10.1016/j.biotechadv.2015.03.012.
6. Pillet, S., Couillard, J., Trépanier, S., Poulin, J. F., Yassine-Diab, B., Guy, B., Ward, B. J. & Landry, N. (2019). Immunogenicity and safety of a quadrivalent plant-derived virus like particle influenza vaccine candidate-Two randomized Phase II clinical trials in 18 to 49 and =50 years old adults. *PloS one*. 14(6), e0216533. https://doi.org/10.1371/journal.pone.0216533.
7. Mackay, C. (2020). Algae tasked with producing COVID-19 test kits. *Phys.org news April 30*. https://phys.org/news/2020-04-algae-tasked-covid-kits.html.
8. Specht, E. A. & Mayfield, S. P. (2014). Algae-based oral recombinant vaccines. Front. *Microbiol*. 5:60. https://doi.org/10.3389/fmicb.2014.00060.
9. Gretler, C. (2020). Tobacco-Based Coronavirus Vaccine Poised for Human Tests. *Bloomberg* May 15, 2020, 6:58 AM EDT.
10. Clinical Trials.gov. (2020). KBP-201 COVID-19 Vaccine Trial in Healthy Volunteers. https://clinicaltrials.gov/ct2/show/NCT04473690?term=Kentucky+BioProcessing&cond=Covid19&draw=2&rank=1.
11. Nogrady, B. (2020). How SARS-CoV-2 Tests Work and What's Next in COVID-19 Diagnostics. *The Scientist*, May 3.
12. Wang, C., Beiss, V. & Steinmetz, N. F. (2019). Cowpea Mosaic Virus Nanoparticles and Empty Virus-Like Particles Show Distinct but Overlapping Immunostimulatory Properties. *Journal of virology*, 93(21), e00129-19. https://doi.org/10.1128/JVI.00129-19.
13. Lopez-Ramirez, M. A., Soto, F., Wang, C. et al. (2020). Built-In Active Microneedle Patch with Enhanced Autonomous Drug Delivery. *Adv Mater*. 32(1), e1905740. https://doi.org/10.1002/adma.201905740.
14. Jain, S. (2020). Virna Therapeutics and University of Toronto Announce Licensing of Neutralizing Monoclonal Antibodies to Treat COVID-19. *Businesswire*, May 27.

Article

Biopharma licensing and M&A trends in the 21st-century landscape

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ABSTRACT

The declining in-house R&D productivity has compelled the biopharmaceutical firms to supplement their innovation pipelines with well-managed licensing or acquisition deals. The reliance on licensed products and acquired technologies continues to increase across the industry to support pipeline expansion and technological diversification. In this article, Licensing and M&A trends across the biopharmaceutical industry are explored by examining the partnering activities of major biopharmaceutical companies and analyzing the trends in the business development transactions of the biotechnology companies worldwide. The information has been extracted from public and proprietary sources such as company annual reports, Industry reports and press releases from biopharmaceutical companies. The transactions data and partnership information has been analyzed over a contiguous twenty-year time period of 2000–2020 to understand the change in strategic focus in dealmaking and trends over the past two decades.

Journal of Commercial Biotechnology (2020) 25(3), 37–51. doi: 10.5912/jcb943

INTRODUCTION

The global pharmaceutical market is estimated to be worth nearly 1,430 billion USD($) by the end of 2020.[1] In the last decade, R&D expenditure of biopharmaceutical companies exceeded half a trillion USD resulting in advances and discoveries that will make a huge difference in millions of patients' lives.[2] In this new era of medicine, many diseases previously regarded as deadly are now manageable and potentially curable. Novartis (10.5), Roche (9.1), Pfizer (7.5), Merck & Co. (7.1), J&J (6.7), Sanofi (6.1), AstraZeneca (5.6) and Glaxo-SmithKline (5.4) are expected to invest more than 5 billion USD on R&D in 2020 with an industry-wide forecasted total R&D spend of USD 160 billion by 2020.[3] In the United States, VC investments in the biopharmaceutical industry have doubled between 2010 and 2015 from $3.7 billion to $8.2 billion.[4] Industry analysts predict that 80% of the revenues for biopharmaceuticals and diagnostics in 2030 will be driven by advances in biologic drugs that were not on the market by 2010.[5]

Pavlou and Belsey have reviewed biopharma licensing and mergers and acquisition (M&A) trends in 2005 where they have discussed the reliance of the leading US and European pharma players on licensing and M&A, types of M&A deals in the industry and their contribution to total M&A value.[6] Gautam et al. have also previously reviewed the key trends in R&D portfolio mix, revenue distribution and operational model over the 1995–2015 period that have impacted and transformed the top 12 big-pharma companies.[7] They concluded that the pharmaceutical companies are adapting their strategic focus towards their areas of strength, consolidating R&D towards hotspots, shifting towards speciality drugs and recognize the emerging markets as major revenue drivers. Third-party collaborations are now an essential part of biopharmaceutical companies' strategy to supplement product pipelines and to maximise revenues using commercial deals.[8] For instance, Boehringer Ingelheim data from 2003 depicted that over two-thirds of sales of three pharmaceutical companies among top 15 were from in-licensed products.[7] This reliance on licensed products and acquired technologies continues to increase across the industry to support pipeline expansion and technological diversification.

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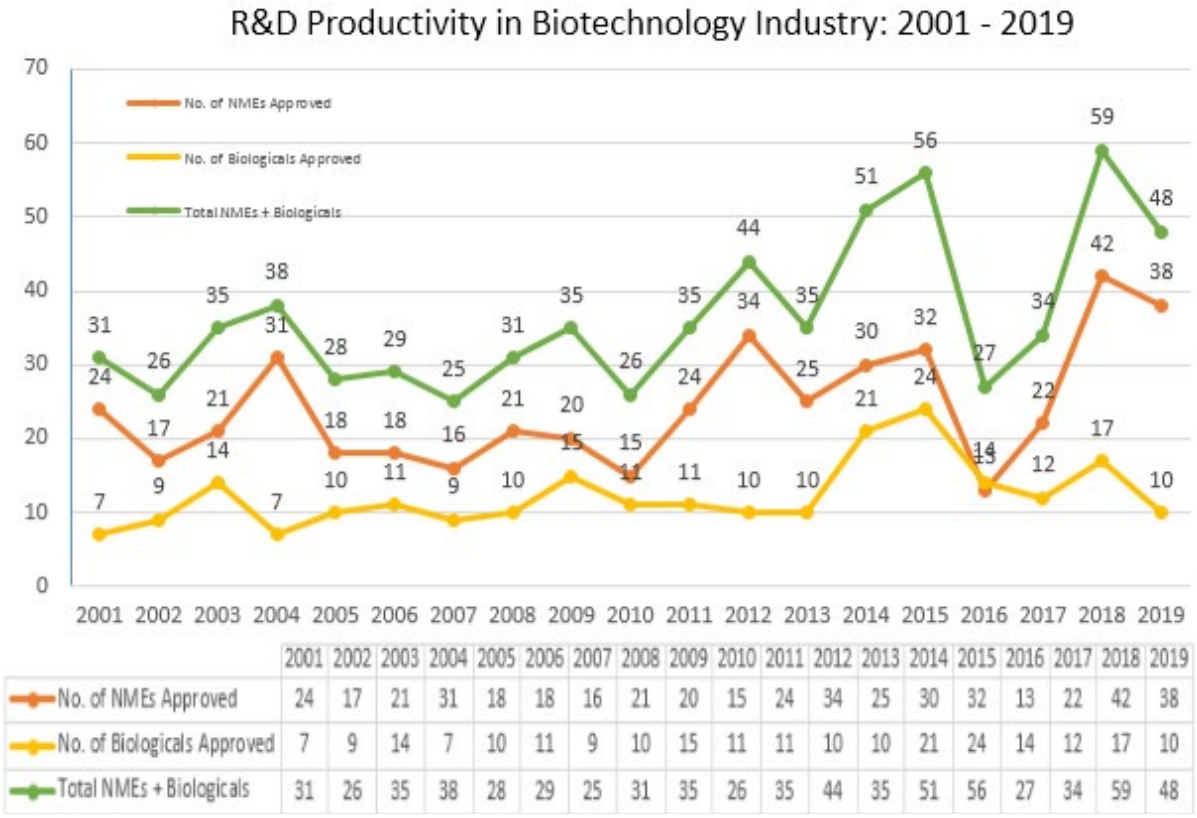

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
No. of NMEs Approved	24	17	21	31	18	18	16	21	20	15	24	34	25	30	32	13	22	42	38
No. of Biologicals Approved	7	9	14	7	10	11	9	10	15	11	11	10	10	21	24	14	12	17	10
Total NMEs + Biologicals	31	26	35	38	28	29	25	31	35	26	35	44	35	51	56	27	34	59	48

Figure 1: R&D productivity in the Biotechnology Industry: 2001 – 2019.

Overview of the relevance of Licensing and M&A in the Biotechnology Industry

Most early-stage biotechnology companies lack sufficient funds and experience to sustain their discoveries through complex and expensive clinical testing and subsequent regulatory approval hurdles. Further, these companies don't have the sales and marketing competence needed to bring their approved drugs swiftly into the market. So, they mostly rely on much larger pharmaceutical companies to finance and conduct clinical testing and to market the drugs once they have received regulatory approval. This is achieved sometimes through a license agreement and sometimes through outright acquisition of the biotechnology pioneer by a larger and better-established pharma company.[9]

Intellectual Property (IP) can be effectively commercialized and exploited through licensing the IP by the owner (the licensor) to another company (the licensee) which would carry out the marketing, distribution and sales activities. 'Licensing Out' an IP means that the licensor retains the ownership of the IP and allows the licensee to use the IP. On the contrary, 'Licensing In' refers to the act of securing rights to use the IP from the licensor by a licensee. Selling IP to a third party is technically known as an 'assignment' where ownership is transferred to a new party with outright disposal of the IP by the owner. In the Biopharmaceutical industry, Spin-out companies are actively involved in Licensing to commercialize research and innovation. This is usually in the form of an exclusive License or an assignment as any company investors may insist that the company should own the IP rights. However, in some cases where the assignment is not feasible, the spin-out company may instead take a sole or non-exclusive licence of the IP. The value, commercialization viability, company strategy and licensing/assignment costs determine the approach adopted in transferring an IP in the Biotechnology sector.

The traditional operational model in big pharmaceutical companies has been that of a fully integrated company. Every operation in R&D, sales and marketing were carried out within the company. Big pharma now lays far greater emphasis on external collaborations to procure and develop new medicines and therapies. In 2010, for example, GlaxoSmithKline's Chief Executive Officer Andrew Witty announced further cuts to the company's in-house R&D organisation, focusing the company strategy towards a "more virtual, more partner-orientated"

model. Witty's remarks echoed with his counterparts across the industry, all now disinvesting from the traditional research model in favour of in-licensing drug candidates while outsourcing development work.[10] The current GlaxoSmithKline's CEO Emma Walmsley has also been focused on creating strategic and operational synergies to build broad industry portfolio while maintaining a leading position in therapeutic areas such as HIV, Respiratory and Pain Relief. The leading big pharma companies such as GSK are likely to continue pursuing external collaborations and in-licensing of technologies with their business development and licensing (BD&L) strategy in the next few decades.

Morgan Stanley economic value analysis report from 2010 also supports divestment of in-house R&D. The report suggests that $1 invested in licensed drugs will on average deliver three times as much value as $1 invested in R&D within the company.[11] Major pharma companies have declared disinvestment in early-stage research in several disease areas in the previous two decades. They are being more reliant on external sources for maintaining their drug innovation pipeline. For instance, in 2010, the same year when Morgan Stanley report was released, AstraZeneca closed down discovery research in 10 therapeutic categories affecting nearly 3500 R&D jobs in the UK, Sweden and the US.

Scope of Business Development deals in the Biotechnology industry

Business development deals in Biotechnology industry fall into one of two broad categories—asset-based and non-asset-based. Asset-based partnerships include acquisitions and licensing of drugs, technology and patented innovations whereas non-asset-based partnerships include Joint ventures, consortia and collaborations where two parties pool resources to achieve a common goal. The types of deals can range from simple patent licensing deals to complex co-development deals, co-promotion deals and commercialisation deals.[12] These collaborative R&D deals (discovery or preclinical-stage) are considered in the licensing section of our study. The motive behind these deals is to develop external collaborations to obtain products to supplement the internal R&D.

In our study, M&A is defined as outright acquisitions that result in the exit of the target firm. However, it must be considered that outright acquisition is one extreme variant of the range of pharmaceutical-biotech and biotech-biotech relationships, including the purchase of a major equity stake (e.g. Roche-Genentech), co-development alliances and co-commercialization or marketing agreements.[13] This continuum of activity makes the definition of merger / acquisition somewhat arbitrary.

Danzon et al. have analyzed the scope, determinants and effects of significant M&A transactions over the period 1988–2000 using a multinomial logit model to test several competing hypotheses to explain the M&A activity across the entire pharma–biotechnology industry.[12] They concluded that pharmaceutical acquisitions of biotechnology companies are consistently driven by an asset-specific motive, such as cross-national acquisitions, assuming that it is a cheaper, quicker and more effective way to buy a local company with established connections rather than building a foreign subsidiary.

The 'valley of death' between drug discovery and its ability to attract formal venture capital has been widening. In particular, venture capital for early-stage biopharmaceutical companies must compete with alternative low-risk profile opportunities that consistently offer high returns in the near-term. Many bioscience venture capitalists are increasingly focusing their investments in emerging life science companies only once their drug candidates enter clinical trials.[14] Finally, it has been evident from previous studies[15,6] that solely trusting the valuations from the hired investment banks for due diligence can be misleading. So, all the large companies now have Business Development & Licensing teams to search, evaluate and negotiate deals.[7] The implementation of a Business development strategy depends on the availability and ability to identify opportunities and execute them at acceptable costs.

KEY LICENSING TRENDS

Reliance on Licensed products and technologies

Post-patent-expiration price competition has become more intense, compelling pharmaceutical companies to either innovate or indulge in Licensing deals to replace innovations in the R&D pipeline. Table 1 provides an overview of the key licensing deals in the biopharmaceutical industry from the 21st century with an overall value of over 500 million USD. We have included only the deals involving a preclinical compound or drugs in advanced clinical trials and excluded discovery stage collaboration deals or commercial rights deals for proper representation of biopharmaceutical dealmaking landscape.

Objectives and nature of the Licensing deals

Companies often employ a licensing strategy for therapeutic areas of challenging scientific nature such as oncology and infectious diseases to hedge against clinical failure. In fact, the proportion of biopharma revenue

Table 1: Key licensing deals from the 21st century.

S.No	Year	Licensee	Licensor	Value	Description
1.	2017	Merck	AstraZeneca	8500 million USD	Strategic oncology collaboration with MSD to co-develop and co-commercialise AstraZeneca's Lynparza for multiple cancer types.
2.	2019	AstraZeneca	Daiichi Sankyo	6900 million USD	License of HER2-targeted antibody-drug conjugate Trastuzumab deruxtecan for breast cancer
3.	2018	Merck	Eisai	5755 million USD	Strategic collaboration for LENVIMA® (lenvatinib mesylate), an orally available tyrosine kinase inhibitor.
4.	2018	Roche	Affirmed	5096 million USD	License to commercialize novel NK cell engager-based immunotherapeutics to treat multiple cancers.
5.	2019	Gilead Sciences	Galapagos NV	5050 million USD	License of phase 3 candidate for idiopathic pulmonary fibrosis known as GLPG1690
6.	2019	GlaxoSmithKline	Merck KGaA	4200 million USD	License of M7824 (bintrafusp alfa) a bifunctional fusion protein-based cancer immunotherapy for solid tumours
7.	2020	AbbVie	Genmab	3800 million USD	License of bispecific drugs led by CD3xCD20 bispecific antibody epcoritamab
8.	2018	BMS	Nektar Therapeutics	3630 million USD	Worldwide license and collaboration for immuno-oncology program, NKTR-214
9.	2018	Gilead (Kite Pharma)	Sangamo Therapeutics	3160 million USD	Exclusive license for cell therapies using zinc finger technology.
10.	2014	Pfizer	Cellectis	2885 million USD	Partnership to develop Chimeric Antigen Receptor T-cell (CAR-T) cancer immunotherapies
11.	2014	Pfizer	Merck KGaA	2850 million USD	Partnership to co-develop and co-commercialize MSB0010718C, an investigational anti-PD-L1 antibody
12.	2019	Roche (Genentech)	Sarepta Therapeutics	2850 million USD	License of Duchenne muscular dystrophy gene therapy SRP-9001
13.	2018	Allogene	Cellectis	2800 million USD	Exclusive license for UCART Cell therapies
14.	2017	Sanofi	Ablynx	2700 million USD	Exclusive worldwide license of Nanobody®-based therapeutics
15.	2019	Gilead Sciences	Nurix	2350 million USD	License of Nurix Protein degradation technology for multiple therapeutic categories
16.	2015	BMS	uniQure	2307 million USD	Global license and commercialization rights for gene therapies against 10 cardiovascular targets
17.	2014	AstraZeneca	Almirall	2095 million USD	Divestment of Almirall's respiratory assets including the marketed drug Eklira plus pipeline candidates.
18.	2015	Sanofi	Regeneron	2000 million USD	License of clinical-stage bispecific antibodies for cancer immunotherapy.
19.	2015	Amgen	Xencor	1745 million USD	License for Xencor's Preclinical CD38 Bispecific T Cell Engager for Multiple Myeloma
20.	2014	BMS	Five Prime Therapeutics	1740 million USD	Partnership to co-commercialize phase I cancer/immunology compound FPA008 and other CSF1R compounds.

21.	2015	Sanofi	Lexicon	1700 million USD	Exclusive license for Sotagliflozin, an oral treatment for Diabetes.
22.	2019	Neurocrine Biosciences	Xenon Pharmaceuticals	1700 million USD	Exclusive licence to Nav1.6 sodium channel inhibitor candidate, XEN901 for epilepsy treatment.
23.	2015	Eli Lilly	Innovent Biologics	1456 million USD	Multiple drug development collaborations to enter Chinese oncology market
24.	2012	Johnson & Johnson	Genmab	1100 million USD	Global license and development agreement for daratumumab (HuMax®-CD38), a human CD38 monoclonal antibody
25.	2016	BMS	Nitto Denko	998 million USD	Exclusive worldwide license agreement for siRNA molecules targeting HSP47
26.	2007	Novartis	Antisoma Plc.	990 million USD	License deal of vascular disrupting agent AS1404 a promising oncology drug
27.	2020	Sanofi	Kiadis Pharma	986 million USD	License deal of K-NK004, modified NK cells to prevent the expression of CD38
28.	2016	BMS	PsiOxus Therapeutics	936 million USD	Exclusive worldwide license of NG-348, a Tumour-Specific Immuno-gene Therapy (T-SIGn)
29.	2016	Takeda Pharmaceuticals	Crescendo Biologics	790 million USD	License for discovery, development and commercialisation of Humabody®-based therapeutics
30.	2017	Sanofi	Principia Biopharma	765 million USD	Exclusive worldwide license of PRN2246
31.	2016	J&J	MacroGenics	740 million USD	Global license to MGD015, a preclinical DART® (dual-affinity re-targeting) molecule for various haematological malignancies and solid tumours
32.	2015	AstraZeneca	Inovio Pharmaceuticals	728 million USD	License agreement for clinical-stage INO-3112 HPV cancer vaccine
33.	2017	BMS	CytomX	723 million USD	Exclusive worldwide license to develop and commercialize Probody therapeutics for eight additional targets.
34.	2017	Biogen	BMS	710 million USD	License of Phase 2 anti-eTau compound for Progressive Supranuclear Palsy.
35.	2007	Sanofi-Aventis	Oxford BioMedica	690 million USD	License of cancer immunotherapeutic TroVax (vaccinia-delivered tumour-associated antigen 5T4)
36.	2007	Schering-Plough	Anacor Pharmaceuticals	625 million USD	License of its phase 2 antifungal ANA2690 retaining the rights to copromote it in the US.

Note: Only Licensing deals with an overall value of over 500 million USD considered. Deals without financial terms have been excluded. Discovery stage collaborative R&D deals and sole Commercial rights deals have also been excluded. Only the deals involving a preclinical target compound or a portfolio of drugs in advanced clinical trials are included in this Table.

generated by in-licensed or acquired compounds rose from 41% in 2005 to 50% in 2014.[16] Generic makers are signing distribution and marketing contracts to reach foreign regulated and developing markets such as the recent out-licensing deals between Pfizer & Aurobindo and GlaxoSmithKline & Dr Reddy's Labs to expand in emerging markets such as India.[17] This trend is expected to increase even further due to a large number of drugs with pending patent expiration in the next few years.

AstraZeneca has been the most prolific pharmaceutical dealmaker in terms of the completed number of deals. AstraZeneca signed a record 169 agreements in total between 2014-2018, 66 of which were out-licensing deals. Such a leading dealmaking rate is also demonstrated when AstraZeneca completed five late-stage deals in 2010, including a 1.24 billion USD deal with Targacept and the 350 million USD acquisition of Novexel, to develop two late-stage antibiotics in partnership with Forest Laboratories.[9]

Table 2: Therapy Area | Projected sales in 2022 (US$B).

S.No	Therapeutic focus area	Average Number of Deals per year	No. of R&D products in 2019	Projected sales in 2022
1.	Oncology	1040	2731	192.2 billion USD
2.	Antidiabetics	430	571	57.9 billion USD
3.	Anti-inflammatory	390*	473	55.4 billion USD
4.	Anti-virals	410*	439	42.8 billion USD
5.	Vaccines	440*	364	35.3 billion USD
6.	Bronchodilators	170*	480	30.1 billion USD
7.	Sensory organs	220	459	28.3 billion USD
8.	Immunosuppressants	370	511	26.3 billion USD
9.	Anti-hypertensives	290	412	24.4 billion USD
10.	Anti-coagulants	210	410	23.2 billion USD
11.	Musculoskeletal	200	461	21.7 billion USD
12.	Dermatologicals	250*	200*	19.9 billion USD
13.	Anti-fibrinolytics	230*	210*	17.1 billion USD
14.	Anti-hyperlipidemics	240*	200*	13.4 billion USD
15.	Anti-bacteria	140	270*	12.8 billion USD
	Top 15	5030	8191	601 billion USD
	Total	5800*	9500*	1100 billion USD

*Source: EvaluatePharma, 2017 for projected sales. IQVIA™ Pharma Deals Half-Year Review of 2018/2019 and Author's calculations for Licensing statistics.*represent estimated projections of global deal count. Note: Deals covering more than one therapeutic area are counted more than once (in each relevant therapeutic area).*

The mean transaction value of licensing deals in 2019 was 455 million USD, a 41% increase from the mean value of 322 million USD in 2018. Also, there was a staggering rise in the value of the mean Upfront payment of the licensing deals, changing 48% from the value of 32.6 million USD in 2018 to 48.3 million USD in 2019.[18] Big Pharma companies signed two-to-three times as many in-licensing agreements as out-licensing deals annually between 2011 and 2015.[19] The majority of the licensing deals throughout the 21st century were in the Discovery and Pre-clinical stages which represent the interest of Licensors in capturing the early-stage assets at a lower price and utilizing the in-house expertise in later developmental stages. In particular, the early-stage deals that offer access to novel technology platforms and next-generation biologics are very popular amongst large pharmaceutical companies. Last year, in 2019, Gilead was the leading dealmaker with three deals collectively worth almost $10 billion. These deals are Gilead Sciences-Galapagos, Gilead Sciences-Nurix and Gilead Sciences-Goldfinch Bio. The Gilead Sciences-Galapagos deal for late-stage idiopathic pulmonary fibrosis (IPF) drugs, in particular, has the biggest upfront payment at $3.95 billion. Gilead has emerged actively in the licensing market with such high-value deals ever since the company recently appointed Gilead's Chief executive Daniel O' Day.

In April 2014, Novartis and GlaxoSmithKline agreed to swap a series of assets where Novartis acquired GlaxoSmithKline's marketed oncology portfolio for $16 billion and sold its vaccines business to GlaxoSmithKline for $7.1 billion, a deal that reshaped two of the world's biggest drugmakers.[20] Similarly, in 2017, Sanofi acquired Boehringer Ingelheim's consumer healthcare (CHC) business in exchange for Sanofi's Animal Health business (Merial). This strategic asset swap was valued at a combined total of 24 billion USD. Such 'Exchange deals' seem to be an attractive alternative for business development transactions in Biotechnology in upcoming years since it helps the firms focus on their key businesses. The big pharma has started to embrace a focused strategic approach on their key therapeutic areas while divesting non-core assets.

Statistics on Licensing deals by sector/ focus area

Oncology, and the field of immuno-oncology in particular, has continued to dominate the dealmaking landscape, while some noteworthy early-stage deal activity for novel biological programmes across a variety of therapy areas was observed throughout the decade. The rise of immuno-oncology as a therapeutic strategy is reflected in the number of licensing deals in the biotechnology industry such as the global strategic Oncology collaboration between Merck and Eisai for LENVIMA©

in 2018. Analysts predict that Oncology will continue to lead all the therapy areas and would represent 17.5% of all Prescription/OTC drug sales by 2022, more than the next three highest therapy areas combined.[21]

The largest CAGR growth in the top 15 therapy categories except Oncology is predicted to be from immunosuppressants, dermatologicals and anti-coagulants.[20] CNS diseases, Infectious diseases, Endocrine diseases and Cardiovascular disease were the next prevalent therapy areas after Oncology for dealmaking. Gene Therapy has also emerged as a top priority focus area in Licensing deals.[17] The global personalized medicine market is forecasted to reach $2.4 trillion with projected sales of $118.15 billion in 2022 at a CAGR of 11.8%, double the projected 5.2% annual growth rate for the overall health care sector. Also, worldwide Medtech sales are forecasted to grow at an annual compound growth rate of 5.1%, reaching US$521.9 billion by 2022 where In-vitro diagnostics is estimated to be the largest Medtech segment with annual sales of US$70 billion by 2022.[20]

Challenges to successful Licensing deals

The expected benefits of the licensing transactions may never be fully realized or may take longer to realize than expected due to 10-15 year development timelines, extensive R&D costs and high rates of scientific & regulatory uncertainty.[15] Also, competition from possible generic or biosimilar alternatives has to be taken into account. When a drug expires from patent protection, the owner loses some market share through generics. For instance, Pfizer lost the US patent protection for their top-selling drug Lipitor in November 2011 which dwindled Lipitor sales from 5 billion USD per year to only 0.93 million USD the year after the patent expired. So, any unforeseen delay such as the COVID-19 pandemic in 2020 can jeopardize the drug development/clinical programs while the nearing patent expiry date would continue to decrease the revenue generated after product launch.

The COVID-19 pandemic has disrupted several other industries such as in the hospitality sector, however, we have witnessed active dealmaking in the pharmaceutical healthcare sector even during this global pandemic. For instance, Gilead acquired cancer drugmaker Forty Seven for $4.9 Billion in April 2020 adding Forty Seven's investigational lead product Magrolimab to their immuno-oncology portfolio. The statistics have shown that the number of deals has been unchanged but the overall deal values and upfront payment values have declined in the second quarter of 2020. Big pharma companies have been resilient in this crisis by redirecting resources towards developing drugs and vaccines against the SARS-CoV-2 virus.

Licensing deals often involve extensive clinical development programs across multiple indications which may involve co-development and co-commercialisation roles between the Licensor and the Licensee. This presents a unique challenge to the licensing dealmaking since adequate involvement of both parties is required for the success of the target product. Furthermore, in recent years, increased access to capital for early-stage companies continues to slow down the licensing activity. The investor sentiment towards biotech companies has been increasingly bullish overall owing to the huge return on investment provided by several blockbuster drugs. Early-stage Biotechnology companies now have a variety of funding options available to them to fund their pipeline programmes for longer. This allows them to retain the rights to their pipelines in the development phase in the hope of achieving higher returns in the clinical stage. Finally, several intangible liabilities such as lawsuits and binding long-term contracts can hamper the licensing or acquisition deals.[14]

Licensing litigation activity and trends

The licensing deals are often disrupted by various lawsuits, claims, government investigations and other legal proceedings that arise in the business development transactions. Such legal proceedings can involve various types of parties such as governments, competitors, customers, suppliers, service providers, licensees, employees, or shareholders. These legal disputes usually involve patent infringement, antitrust, securities, pricing, sales and marketing practices, environmental, commercial, contractual rights, licensing obligations, health and safety matters, consumer fraud, employment matters, product liability and insurance coverage.[22] Moreover, failure to enforce the patent rights likely results in substantial decreases in the respective product revenues from generic competition.

Last year in 2019, Sanofi terminated a 1.7 billion USD licensing deal with Lexicon Pharmaceuticals due to unsatisfactory results in Phase III trials of Sotagliflozin. Lexicon accused Sanofi of 'breach of contract' by ending the partnership. Sanofi has contractual obligations to fund ongoing clinical trials for a specified period following termination as per documents with US SEC. This incident has shown the importance of properly discussing and agreeing upon the restrictions and obligations involved in any licensing deal in case of deal termination. The same year, Amgen and Novartis entered a legal dispute regarding the collaboration agreements of the migraine drug Aimovig (FDA approved drug). Amgen

terminated the partnership alleging that Novartis was in breach of the collaboration agreements for entering into a new joint development agreement with Alder BioPharmaceuticals, innovating a potential rival to Aimovig. However, Novartis accused Amgen of attempting to back out of their partnership and keep all the profits from the drug's sales and considered the notice of termination "unjustified and without legal merit".[23] Here the conflict arose due to Novartis' involvement with Alder's development of a similar drug to Aimovig, so the Licensing and M&A deals should avoid any overlapping projects to avoid litigations.

Every deal structure carries different tax and accounting implications. M&A, for example, may add tax benefits if the target company bears net operating losses. Also, R&D incentives can be utilized to reduce cash taxes by the acquiring company. However, M&A can negatively impact financial statements because it requires consolidation of assets, liabilities, and other financial items of two or more entities into one.[15] Proper due diligence should unearth any issues which can cause legal disputes after the completion of any deal. Furthermore, Risk management through the use of IP Insurance can be very helpful for firms involved in Licensing deals.

Strategies for successful licensing deals

Initial stage assignment deals usually provide the least return in the longer term, as IP tends to become more valuable as it is developed further and commercialized. Besides, the valuation of early-stage innovations is very challenging which increases the risk involved in selling an IP at an undervalue or overpaying for an economically unrewarding IP. However, Licensing has shown a satisfactory track record for early-stage patented innovations. Licensing out of an IP minimizes the capital investment and maximizes the return on IP for the owner by creating an additional income stream while retaining the ownership. Out-licensing has also emerged as a viable option to offload non-core assets and share development risks.

An established firm already has its own marketing team, salesforce, distribution channels and a well-respected brand and reputation. These will enable it to access the market for an IP product very effectively; by contrast, commercialising the IP through a start-up company will require the IP owner to create his access to the marketplace from scratch. In such situations, an optimal licensing deal is a win-win for both parties. Financial rewards from successful licensing are usually not immediate but can build up to respectable levels over the years. Therefore, a Business Development Executive can seek to reduce the cash at risk by using deal structures that make payment contingent upon hitting specific milestones.

Another important strategy is to negotiate licenses with the technology transfer offices within the research institutions. This would enable companies to invest in potential early-stage inventions at a much lower capital investment which can be financially very rewarding. So for advancing biopharmaceutical innovation, academic collaborations should be an integral part of the business development strategy. For instance, Merck & Co. have launched academic partnerships with universities and academic institutes, such as the California Institute for Biomedical Research (Calibr), to accelerate the commercialization of academic research.[3]

Current practices in due diligence are varied across the Biotechnology industry. For example, Bristol-Myers Squibb ranking of potential Licensing deals is based on three measures: Probability of technical and regulatory success, Expected NPV and Risk-adjusted Internal rate of return calculated for each asset.[24] Novo Nordisk and Celgene were ranked top with best positive partnering attributes in BCG survey of Biotechnology CEOs and Licensing Executives, 2012 reflecting the trend towards inclination of Big-pharma to partner with these two companies.[25] Also, the survey indicated that GSK, Merck and Roche were the preferred buy-side companies for licensors. Thus, the partnering characteristics of a company also influence the business development deals in the biotechnology industry.

KEY M&A TRENDS

Reliance on M&A in Biotechnology/ Pharma companies

Big pharmaceutical companies use M&As to access strategically important intellectual property (IP), enter new therapeutic areas and fill R&D pipeline gaps in the company. Major pharmaceutical companies have broadened their R&D portfolio by accessing research projects and drug candidates from Mergers and acquisitions of external sources. M&A activity in the pharmaceutical–biotechnology industry during the last decade of the 20th century (1988-2000) had exceeded 500 billion USD.[12] Whereas, the aggregate value of all M&A deals in 2010-2020 has exceeded 1200 billion USD.[17,26]

Objectives and nature of the M&A deals

The mean transaction value of M&A deals was 2690 million USD in 2019 compared to 1613 million USD in 2018

Table 3: Key M&A deals from the 21st century.

S.No	Year	Parent Company	Target Company	Value (in billion $)	Description
1	2000	Pfizer	Warner-Lambert	111.8	Pfizer acquired Warner-Lambert and gained product lines such as Parke-Davis branded pharmaceuticals
2	2000	Glaxo Wellcome Plc	SmithKline Beecham	76.0	Merger of two UK-based drugmakers to form the new company known as GlaxoSmithKline
3	2019	Bristol-Myers Squibb	Celgene	74.0	Definitive merger agreement expected to achieve $2.5 Billion Run-Rate Cost Synergies by 2022
4	2004	Sanofi	Aventis	73.5	Birth of Sanofi-Aventis by merger of France's largest drugmaker.
5	2015	Actavis	Allergan	70.5	The merger provided dominant position in segments like Eyecare, Neurosciences, Dermatology, Gastroenterology and Urology
6	2009	Pfizer	Wyeth	68.0	Merger for Diversification of the in-line and pipeline patent-protected portfolio of biopharmaceuticals
7	2003	Pfizer	Pharmacia	64.3	Pfizer-Pharmacia merger was fueled by the Arthritis drugs Celebrex and Bextra, which were expected to have $3.75 billion in sales per annum
8	2018	Takeda Pharmaceutical	Shire	62.0	Acquisition focused on four therapeutic areas – Oncology, Neuroscience, Rare diseases and Plasma-derived therapies
9	2016	Bayer	Monsanto	54.5	Acquisition to create the world's biggest agro-chemical and seed company
10	2010	Novartis	Alcon	52.5	Novartis expands reach in eye-care business by buying Alcon shares from Nestlé
11	2009	Merck & Co.	Schering-Plough	47.1	A reverse merger to obtain market rights for Infliximab (Remicade)
12	2009	Roche	Genentech	46.8	Consolidated 1990 acquisition of Genentech
13	2014	Medtronic	Covidien	42.3	Mergers of two giants in medical device community – Spinal Implants, Heart devices and Insulin pumps
14	2015	Teva Pharmaceutical Industries	Actavis	40.5	Increased scale and pricing power in the generics market was the deal driver.
15	2016	Shire	Baxalta	32.0	Merger focused on rare disease products – HAE, Endocrine diseases and lysosomal storage diseases.
16	2017	Johnson & Johnson	Actelion	30.0	Four focused therapeutic areas: Cardiovascular disorders, CNS disorders, Immunological disorders and Orphan diseases.
17	2006	Boston Scientific Abbott Laboratories	Guidant	27.2	Merger for medical devices portfolio especially cardiovascular devices
18	2000	Pharmacia & Upjohn	Monsanto	25.2	The company retained Monsanto's pharmaceutical division (Searle) and spun off the remaining interests
19	2017	Abbott Laboratories	St Jude Medical	25.0	Merger to create a diverse portfolio of devices, diagnostics, Nutritionals and branded generic pharmaceuticals
20	2015	AbbVie	Pharmacyclics	21.0	Focus on Imbruvica® (ibrutinib), a Bruton s tyrosine kinase inhibitor approved for the treatment of certain B-cell malignancies
21	2014	Actavis	Forest Laboratories	20.7	Merger to Strengthen Actavis' Specialty Brands Business
22	2011	Sanofi	Genzyme Corporation	20.1	France's pharmaceutical company Sanofi acquisition of Genzyme is symbolic of the Pharma shift into Biotechnology

23	2012	Johnson & Johnson	Synthes	19.7	Synthes integrated with DePuy franchise to establish the DePuy Synthes Companies of Johnson & Johnson.
24	2006	Bayer	Schering	18.4	Created Bayer-Schering Pharmaceuticals headquartered in Berlin
25	2016	Quintiles	IMS Health	17.6	Created IQVIA, one of the world's largest contract research organizations
26	2015	Pfizer	Hospira	17.0	Expanded business in Injectable drugs, Biosimilars and Infusion technologies market
27	2015	Merck Group	Sigma-Aldrich	17.0	New entity to enhance product range, capabilities and geographic reach
28	2001	Amgen	Immunex	16.8	Immunex's key product Enbrel, a rheumatoid arthritis drug was a key driver
29	2006	Johnson & Johnson	Pfizer Consumer Health	16.6	All-cash transaction which provided a boost to global personal care and OTC medicines business
30	2014	Novartis	GlaxoSmithKline Oncology	16.0	Newly-acquired therapies such as Tafinlar®, Votrient® and Promacta®
31	2015	Valeant	Salix Pharmaceuticals	15.8	Created a new speciality platform for growth in U.S. Gastrointestinal Market
32	2007	AstraZeneca	MedImmune	15.6	Acquisition of U.S. biotechnology company MedImmune to expand towards vaccines and biologicals
33	2007	Schering Plough	Organon International	14.5	The acquisition added five drugs in Phase III development
34	2014	Bayer	Merck & Co Consumer Health	14.2	The acquisition significantly enhanced Bayer's OTC business across multiple therapeutic categories and geographies
35	2016	Pfizer	Medivation	14.0	Acquired promising late-stage oncology pipeline to accelerate position in Oncology
36	2015	Zimmer Inc.	Biomet Inc.	13.4	Created the Zimmer Biomet Holdings, a leader in musculoskeletal healthcare market
37	2019	Amgen	Otezla (drug programme)	13.4	Otezla® (apremilast) acquired from Celgene in connection with its merger with Bristol-Myers Squibb
38	2006	Merck Group	Serono	13.2	Merck's Pharma Ethicals division combined with Serono to create Merck-Serono Biopharmaceuticals
39	2018	GlaxoSmithKline	Novartis Consumer Healthcare	13.0	Buyout of Novartis' 36.5% stake in the Consumer Healthcare Joint Venture
40	2017	Gilead Sciences	Kite Pharma	11.9	Acquisition aimed to position Gilead as a Leader in Cell Therapy
41	2018	Sanofi	Bioverativ	11.6	Creating a Leading Hemophilia Portfolio by acquiring therapies in rare blood disorders.
42	2019	Pfizer	Array BioPharma	11.4	Acquisition to bolster cancer treatment portfolios
43	2011	Gilead Sciences	Pharmasset	11.2	Acquisition directed towards the promising Hepatitis C treatment portfolio
44	2013	Amgen	Onyx Pharmaceuticals	10.4	Oncology Portfolio and Pipeline such as Multiple Myeloma drug Kyprolis® were the key deal driver
45	2019	Novartis	The Medicines Company	9.7	Inclisiran was the target drug to expand cardiovascular disease R&D portfolio

Source: Mergers and Innovation[8] and Media release event study by the author. Note: We have NOT considered Net Present value (NPV) of the deals and the actual deal figures are shown. Only deals with an overall value above 9 billion USD have been considered.

indicating a positive trend in dealmaking activity across the industry.[17] Pfizer has been the most active in BD&L transactions in the first decade of the 21st century with some high-value M&A deals. Pfizer acquired three large companies — Warner-Lambert (in 2000), Pharmacia (in 2003) and Wyeth (in 2009) — and multiple smaller companies, such as Vicuron, Rinat and Esperion to meet its business objectives.[27] However, in the second decade, acquisitions were largely driven by the strategic rationale to build complementary capabilities rather than a desire to be massive.[6] For instance, AbbVie acquired Pharmacyclics to enhance AbbVie's scientific and commercial presence in Oncology with the addition of Imbruvica®, a blockbuster drug approved in multiple indications for blood cancers.

In March 2009, Roche announced a $46.8 billion deal to acquire full ownership of Genentech which has been a key drug industry merger.[28] This acquisition was strategically directed towards Genentech's three best-selling products — the cancer drugs Avastin, Herceptin and Rituxan. Their Swiss rival Novartis AG. announced $39 billion takeover of U.S. eye care company Alcon the same year. Also, in the 'merger wave' of 2009, Pfizer acquired Wyeth for $68 billion, while Merck paid $41 billion to acquire Schering-Plough to diversify their pipeline with the addition of Remicade and Simponi.

Mergers can intensify the research performance of the firms by creating large knowledge synergies, optimizing R&D expenditure and improving the research productivity.[29] The M&A dealmaking trends indicate that the big pharma has transitioned into a leaner and focused model by divesting non-core assets and focusing on their speciality therapeutic areas. In 2019, Bristol-Myers Squibb acquired Celgene for a massive 74 billion USD because of enhanced margins, highly complementary portfolios, strong combined cashflows and revenue potential of more than 15 billion USD of six near-term product launches. Therefore, in such cases, the resulting synergies in R&D, administrative and market from an M&A deal usually make the resulting combined company greater than the 'sum of the parts'.

Mean upfront payments for clinical-stage assets have also increased markedly over the 2011-2015 time period.[30] However, discovery and preclinical projects continue to be popular among dealmakers. The level of M&A and licensing activity for preclinical assets has been dominant over the deal volume for clinical or approved products. Also, the dealmaking activity for Phase I and Phase II assets was lower than Phase III and pre-registration assets which demonstrates the reluctance of investors in cashing-in on the riskier Phase I and II projects. Some may argue that the trend of sole interest in late-stage innovations is detrimental to drug discovery in Biotechnology industry because then fewer funds are available for early-stage research projects. However, owing to the very low success probability (<5%) of drug development projects, such early-stage projects should be funded primarily by government and philanthropic organizations. This ensures that a single company does not bear any loss for undertaking drug discovery initiatives and the underlying risk is shared by the use of public funds. On the contrary, the pharmaceutical companies should focus their investments and resources in accelerating late-stage projects by adopting rigorous licensing and acquisition strategies. The logic of comparative advantage strongly favours "Big Pharma" companies in acquiring late-stage projects. So, this current financial landscape at various stages of drug development does facilitate innovation with more emphasis towards bringing the medicine to market.

Statistics on M&A deals by sector/focus area

The inclination towards Oncology is reflected in a recent acquisition of Array Biopharma by Pfizer for 11.4 billion USD to enrich Pfizer's R&D pipeline with high-potential targeted investigational cancer therapies such as BRAFTOVI® and MEKTOVI® for metastatic colorectal cancer.[31] In 2018, a wave of M&A deals emerged in Oncology such as 9 billion USD acquisition of Juno Therapeutics by Celgene and 5 billion USD acquisition of Tesaro by GlaxoSmithKline.[32] Oncology remained a priority but other areas of research that gained momentum in both licensing and M&A were Neuroscience, Infectious diseases, Cardiovascular and Gene therapies.[18]

The first decade of the 21st century had deals directed towards diversification into new therapeutic areas and were majorly driven by key blockbuster drugs that could provide entry into a new therapeutic area. For instance, Merck succeeded with the transformational acquisition of Serono in 2007 driven by blockbuster drugs such as Rebif®, a treatment for relapsing-remitting multiple sclerosis. Similarly, Merck & Co. had a reverse merger deal with Schering-Plough in 2009 which doubled their number of late-stage drugs in development. New innovative therapies emerged in the second decade such as Cell-based therapies in 2011 with Provenge and Gene-based therapies in 2012 with Glybera. In the recent years, the total value of Medtech venture financing deals has increased drastically, since exponential advances in Machine Learning and Artificial intelligence (AI) technology has converged digital health technologies with Medtech which has attracted more venture capital investment.[20] Similarly, M&A deals relating to biomarkers, biosensors and companion diagnostics were also

Table 4: Key products from M&A and Licensing deals for top 20 biopharma companies.

S.No	Company	Products / Technologies	Net Sales (2019)
1.	Roche	Ocrevus®, Hemlibra®, Alecensa®, RoActemra®	53.36 billion USD
2.	Pfizer	Eliquis®, Enbrel®, XTANDI®, Celebrex®	51.75 billion USD
3.	Novartis	Promacta®, Jakavi®, Lucentis®, Gilenya®	47.44 billion USD
4.	Merck & Co.	KEYTRUDA®, BRIDION®, SIMPONI®	46.80 billion USD
5.	GlaxoSmithKline	Zejula®, BREO™ ELLIPTA™	44.17 billion USD
6.	Sanofi	Lemtrada®,Libtayo®,Eloxatin®, Aubagio®	42.78 billion USD
7.	Johnson & Johnson	IMBRUVICA®, DARZALEX®, INVOKANA®	42.19 billion USD
8.	AbbVie	Humira®, Mavyret®, Imbruvica®	33.26 billion USD
9.	Takeda	VELCADE®, ADYNOVATE®, TRINTELLIX®	30.87 billion USD
10.	Bristol-Myers Squibb	OPDIVO®, Eliquis®, YERVOY®, EMPLICITI®	26.14 billion USD
11.	AstraZeneca	CRESTOR®, Lumoxiti™, FARXIGA®, ONGLYZA®	24.38 billion USD
12.	Amgen	KANJINTI™, Otezla®, KYPROLIS®, Aimovig™	23.36 billion USD
13.	Boehringer-Ingelheim	Trajenta®, JARDIANCE®, BASAGLAR®	22.49 billion USD
14.	Gilead	YESCARTA®, HARVONI®, Nurix DELIGASE™	22.45 billion USD
15.	Eli Lilly & Co.	Humalog®,VITRAKVI®,QBREXZA®	22.31 billion USD
16.	Bayer	EYLEA®, NEXAVAR®, BETAFERON®	21.27 billion USD
17.	Novo Nordisk	Macrilen™, INDiGO®, Dicerna GalXC™	18.29 billion USD
18.	Teva	Truxima®, BENDEKA®, Attenukine™	16.88 billion USD
19.	Biogen	TECFIDERA®, Spinraza®, Tysabri®	14.37 billion USD
20.	Otsuka	Visterra HIEROTOPE®, ABILIFY MYCITE®, REXULTI®	13.11 billion USD

Source: Company Annual Reports 2019. Only Pharmaceutical division is considered for net sales(in billion USD).

very popular. New alliances with Artificial intelligence (AI) technology developers to accelerate drug discovery and improve R&D productivity and efficiency have become more common. For example, AstraZeneca collaborated with BenevolentAI in 2019 to use AI and Machine Learning for the discovery and development of new treatments for chronic kidney disease and Idiopathic pulmonary fibrosis.

Challenges to successful M&A deals

Big mergers reshape the R&D and growth of the therapeutic areas targeted in M&A strategy. They are likely to rise anticompetitive concerns and may provide fewer incentives to innovate in the long-run.[27] Licensing deal involves working with a licensor who is committed to the continued success of the asset. Such a structure creates more accountability for both the licensee and licensor to hit key milestones in the development and launch of the asset. However, In M&A, if the strategic focus of the acquiring company changes, the assets could linger in development pipelines without being progressed or terminated, especially in phase I or II.[15]

In 2015, Pfizer attempted to acquire Allergan Biologics Ltd, the maker of Botox for 160 billion USD which would have been the largest pharmaceutical deal ever.[33] The plan was to move Pfizer to where Allergan was located in Ireland so that the company could pay the Irish corporate tax rate of 12.5% instead of America's 35% corporate rate. The deal was contingent on several factors including shareholder agreement, US and EU approval. This deal was structured as a reverse merger so that the smaller Allergan was technically acquiring the much larger Pfizer.[33] However, the deal ultimately fell through because of new laws that were introduced by U.S. President Barack Obama to limit corporate tax inversions.

Furthermore, Key talent or capabilities could be lost in M&A transactions, potentially disrupting R&D with a substantial negative impact on the momentum of research programmes.[15,8,27] The integration demands of acquisition must not be underestimated, and a thoughtful post-merger integration planning should be implemented for the success of the acquired assets. Finally, novel and highly sought-after assets are usually tied up in licensing agreements with other companies early on in development, which causes acquisition deals to be overpriced to gain majority equity of the Intellectual property.

Corporate Strategies for successful M&A deals

The percentage of the profit received by both parties in a Merger situation will be less than if the initial owner were to commercialize the IP solely, as the financial rewards will be shared between the partners. So, if the IP owner is confident with the success of the IP and has the economic resources to commercialize the IP by itself then diluting the profits by a Merger with another company should be avoided. However, only if the Merger adds extra value to the commercialization of IP such as market penetration into new geographical locations/access to new customer segments which compensates for the ownership share loss, the owner should proceed towards a Merger deal. The deals where multiple assets are involved, such as Megamergers are complicated to evaluate but offer a balanced R&D portfolio.

Often a Life Sciences IP will require extensive R&D and a large Infrastructure to be developed and enhanced, which is very expensive. Also, commercialization of this IP may require complementary IP, products and services which are present and owned by established firms. In these circumstances, it makes sense to seek to place the IP in that context through M&A, rather than try to raise capital via a spin-out company and ultimately to compete with established players. Therefore, M&A is an optimal exit strategy for small firms in such situations.

Biopharma companies should consider thorough due diligence and integration planning in advance of the transaction to help increase the success of assets sourced through M&A.[15] M&A should be strategically used to expand the number of projects in R&D portfolio to compensate for individual project failures and maximize ROI expected by investors. Currently, the corporate R&D pipelines of the top companies include more than 150 drug projects in development phases, with GSK (261), Roche (248), Novartis (223), and Pfizer (205) having more than 200 drug projects in their portfolio.[34]

CONCLUSION

In conclusion, over this decade, there have been numerous suggestions of the radical ways in which pharma industry can re-structure itself. Critics have suggested that big pharma companies should go so far as to divest themselves completely of all R&D functions, and simply become companies which acquire new drugs and then market them. The previous trends have indicated that late-stage licensing deals have been a priority for large pharma over preclinical licensing deals.[6] This shift in focus from in-house research to late-stage deals is also reflected from the current trends in Licensing and M&A from Table 1 and Table 3. However, in the past 15 years, the M&A and licensing activity for preclinical assets has been dominant over the deal volume for late-stage or approved products. Therefore, most of the big pharma companies have reshaped their BD&L strategy towards creating strategic and operational synergies to bolster their drug pipeline at the preclinical level.

The pressure from investors to launch new products, imminent blockbuster patent expiries and fewer returns from in-house R&D spending has caused the major pharma companies to remain dependent on licensing and M&A deals for supplementing their innovation pipelines. We expect this reliance on licensed products and technologies will continue to increase in the next few decades because of the increasing complexity of innovations in biotechnology can never be sufficiently addressed without external collaborations. Each pharma company does maintain their excellence and leadership in certain therapeutic areas but the firms need external innovations to stay competitive in the biopharmaceutical industry. We also observed a continued inclination towards Oncology in both Licensing and M&A deals which is reflected in the higher deal count and mean deal value of Oncology deals. However, other promising areas in dealmaking were CNS diseases, Infectious diseases, Endocrine diseases and Cardiovascular diseases. Digital health technologies and Medical devices have also have emerged as promising areas for M&A and Licensing.

The current forecasts suggest that Novartis, Pfizer and Roche would dominate the pharmaceutical market with expected sales of $49.8 billion, $49.7 billion and $49.6 billion respectively by 2022.[35] So, these three companies are expected to be the key players in M&A deals for the next few years. A previous study showed that for deals executed between 2007 and 2012, a greater percentage of assets sourced through licensing (22%) made it to market than assets sourced through M&A (%).[15] This is a result of higher accountability in a Licensing deal and a drive to hit the key milestones to gather the next stage funding inherent to the Licensing deal structures. Out-licensing of non-core assets would continue to be significant in the next few decades while we project the in-licensing of new innovative products and technologies to be more prominent in the future. So, commercial biotechnology projects directed towards the development of novel technologies are likely to be preferred for in-licensing or acquisition. For instance, recently, AbbVie entered into a collaboration with Genmab for three of Genmab's next-generation bispecific antibody products, including Epcoritamab.

Scenario planning using the Licensing and M&A data from this review could help organizations deal with uncertainty and prepare for the future. The best deals are

likely to bring synergies in therapeutic areas and build on a life sciences company's strengths. Divestitures, in the areas where a life sciences company is weak or where an acquisition is not performing, are likely opportunities for growth. Pharma licensing and acquisition deals are now far more flexible and creative with opportunities to capture value through co-development / co-marketing rights and retaining geographical rights in the deal.[36] Therefore, the licensors can shift from pure licensing deals to deals involving retention of commercial and geographical rights. A key challenge in M&A and Licensing over the coming decade will be external collaborations to expand the sales into the emerging markets which have shown to be a major contributor in the big pharma revenue. Finally, wisely-positioned licensing deals by pharma companies that complement their R&D innovation synergistically would be important in deciding their market capitalization growth in the biopharmaceutical industry.

ACKNOWLEDGEMENT

I thank the University of Manchester for their support by Dean's Doctoral Scholar Award and President's Doctoral Scholar Award. I also thank my PhD supervisor, Dr Robin Curtis, for his mentorship and guidance and members of the Curtis lab for their enduring support.

REFERENCES

1. International Federation of Pharmaceutical Manufacturers & Associations. (2017). The Pharmaceutical Industry and Global Health, https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf, accessed 26 April 2020.
2. Pharmaceutical Research and Manufacturers of America (PhRMA). (2019). Pharmaceutical Industry Profile 2019, https://www.phrma.org/en/Report/Industry-Profile-2019, accessed 5 November 2019.
3. Schuhmacher, A., Oliver, G. & Markus, H. (2016). Changing R&D models in research-based pharmaceutical companies. *Journal of translational medicine.* 14.1: 105, https://doi.org/10.1186/s12967-016-0838-4.
4. TEConomy Partners; for PhRMA. (2017). Closing the Gap: Increasing global competition to attract and grow the Biopharmaceutical sector, https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMA-InternationalReport-vfinal.pdf, accessed 26 April 2020.
5. OECD. (2009). The Bioeconomy to 2030: Designing a Policy Agenda, OECD Publishing, Paris, https://doi.org/10.1787/9789264056886-en.
6. Pavlou, A. K. & Mark, J. B. (2005). BioPharma licensing and M&A trends. *Nat Rev Drug Discov.* 4, 273–274. https://doi.org/10.1038/nrd1697.
7. Gautam, A. & Xiaogang, P. (2016). The changing model of big pharma: impact of key trends. *Drug discovery today.* 21.3: 379-384, https://doi.org/10.1016/j.drudis.2015.10.002.
8. Davies, R. (2013). The relevance and importance of business development and licensing in the biopharmaceutical industry. *Journal of Commercial Biotechnology.* 19.3, https://doi.org/10.5912/jcb592.
9. Comanor, W. S. & Frederic, M. S. (2013). Mergers and innovation in the pharmaceutical industry. *Journal of health economics*. 32.1 (2013): 106-113, https://doi.org/10.1016/j.jhealeco.2012.09.006.
10. Pharmafile. (2010). R&D: a new world order, http://www.pharmafile.com/news/r-and-d-new-world-order, accessed 10 December 2019.
11. Morgan, S. (2010). Pharmaceuticals Exit Research and Create Value. New York: Morgan Stanley Research Report.
12. Drug Development and Delivery. (2017). R&D Partnerships, https://drug-dev.com/rd-partnerships-partnering-for-progress-how-collaborations-are-fueling-biomedical-advances/, accessed 28 April 2020.
13. Danzon, P. M., Andrew, E. & Sean, N. (2007). Mergers and acquisitions in the pharmaceutical and biotech industries. *Managerial and Decision Economics.* 28.4-5 (2007): 307-328, https://doi.org/10.1002/mde.1343.
14. Pharmaceutical Research and Manufacturers of America (PhRMA). (2017). Driving Innovation and Economic growth for the 21st century, http://phrma-docs.phrma.org/files/dmfile/PhRMA-Driving-Innovation_06_01.2017.pdf, accessed 21 February 2020.
15. John, I. (1998). Mergers and Acquisitions in the Pharmaceutical and Biotech Industries. Master thesis, Sloan School of Management, Cambridge, Massachusetts.
16. Deloitte. (2017). External innovation. How biopharma companies are bolstering R&D pipelines through deal-making, https://www2.deloitte.com/us/en/insights/industry/health-care/biopharma-companies-deals-research-development.html, accessed 26 April 2020.
17. PricewaterhouseCoopers. (2011). India Pharma Inc.: Capitalising on India's Growth Potential, https://www.pwc.in/assets/pdfs/publications-2011/pwc_cii_pharma_summit_report_22nov.pdf, accessed 26 April 2020.

18. Heather, C. & Natasha, P. (2020). IQVIA PHARMA DEALS: Half-Year Review of 2019. IQVIA.

19. Amanda, M. (2016). Datamonitor Big Pharma Licensing Trends. Informa Pharma Intelligence.

20. BBC. (2014). Novartis and GSK to exchange assets and launch joint venture, https://www.bbc.co.uk/news/business-27107416, accessed 26 April 2020.

21. Deloitte. (2018). 2018 Global life sciences outlook, https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-ls-outlook-2018.pdf, accessed 26 April 2020.

22. Bristol-Myers, S. (2018). Annual Report, https://s21.q4cdn.com/104148044/files/doc_financials/annual_reports/2018/2018-BMS-Annual-Report.pdf, accessed 12 January 2020.

23. FiercePharma. (2019). As Amgen seeks to can Aimovig collaboration, Novartis sues to save the deal, https://www.fiercepharma.com/pharma/not-quite-a-year-into-launch-amgen-wants-to-can-its-aimovig-collaboration-novartis-lawsuit, accessed April 26 2020.

24. Kazuo, E. & Bristol-Myers, S. (2004). Pharmaceutical Portfolio Management, Talk at DAAG.

25. Boston Consulting Group. (2014). 2014 BCG Biopharma Partnering Survey and Benchmarking, https://www.bcg.com/industries/Biopharmaceuticals/bcg-biopharma-partnering-survey-benchmark.aspx, accessed 26 April 2020.

26. Heather, C. & Natasha, P. (2019). IQVIA PHARMA DEALS: Half-Year Review of 2018. IQVIA.

27. LaMattina, J. L. (2011). The impact of mergers on pharmaceutical R&D. *Nature Reviews Drug Discovery.* 10.8 (2011): 559, https://doi.org/10.1038/nrd3514.

28. Andrew, P. (2009). Roche Agrees to Buy Genentech for $46.8 Billion. The New York Times, https://www.nytimes.com/2009/03/13/business/worldbusiness/13drugs.html, accessed 26 April 2020.

29. Ornaghi, C. (2009). Mergers and innovation in big pharma. *International journal of industrial organization.* 27.1 (2009): 70-79, https://doi.org/10.1016/j.ijindorg.2008.04.003.

30. Heather, C. & Taskin, A. (2016). IMS PharmaDeals Review of 2015. IMS Health.

31. Pfizer. (2019). Pfizer to acquire Array Biopharma, https://www.pfizer.com/news/press-release/press-release-detail/pfizer_to_acquire_array_biopharma, accessed 26 April 2020.

32. Informa Pharma intelligence. (2019). Pharma R&D Annual Review 2019, https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2019/files/whitepapers/pharma-rd-review-2019-whitepaper.pdf, accessed 26 April 2020.

33. Reuters. (2016). Obama's inversion curbs kill Pfizer's $160 billion Allergan deal, https://uk.reuters.com/article/uk-allergan-m-a-pfizer/obamas-inversion-curbs-kill-pfizers-160-billion-allergan-deal-idUKKCN0X22E1, accessed 26 April 2020.

34. Citeline. (2014). Pharma R&D annual review, http://maxicool5.free.fr/Bourse/Valo%20Pharma/Annual-Review-2014b.pdf, accessed 26 April 2020.

35. Evaluate Pharma. (2017). World Preview 2017, Outlook to 2022, https://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf, accessed 13 February 2020.

36. Moran, N. (2007). Licensing deals morph to acquisitions in seller's market. Nat Biotechnol 25, 609–610, https://doi.org/10.1038/nbt0607-609.

Article

COVID-19 Diagnostic Testing: Lessons Learned for Innovative Product Development During A Public Health Emergency

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ABSTRACT

In response to the Coronavirus Disease-2019 (COVID-19) pandemic, the U.S. Food and Drug Administration (FDA) used its emergency authority through Emergency Use Authorizations (EUAs) to make COVID-19 in vitro diagnostic tests widely available to both diagnose active infection and help identify individuals with an adaptive immune response indicating recent or prior infection. Hundreds of innovative tests were quickly developed under Section IV.D. of FDA's Policy for Diagnostic Tests for Coronavirus Disease-2019. National reimbursement guidance through Centers for Medicare & Medicaid Services (CMS) provided significant financial incentives to track the endemic and enable healthcare workers and others get back to work more quickly. The US market for tests grew rapidly and the now exceeds $15 billion. However, many issues regarding product quality and availability have plagued the industry and called into question FDA's policy and regulatory framework for allowing these tests to be commercially available. This paper analyzes the development of COVID-19 in vitro assays and the lessons learned for innovation during a public health crisis.

Journal of Commercial Biotechnology (2020) 25(3), 52–61. doi: 10.5912/jcb944
Keywords: COVID-19; diagnostic testing; public health

BACKGROUND

In early January 2020, a novel coronavirus SARS-CoV-2, which causes COVID-19, was identified as the infectious agent causing an outbreak of viral pneumonia in Wuhan, China, where the first cases had their symptom onset in December 2019 [1]. Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and cause respiratory, enteric, hepatic, and neurologic diseases [2]. Seven coronavirus species are known to cause human disease. Four viruses (229E, OC43, NL63, and HKU1) are prevalent and typically cause common cold symptoms in immunocompetent individuals. Three other strains include Severe Acute Respiratory Syndrome Coronavirus (SARS-COV-1 and SARS-CoV-2) and Middle East Respiratory Syndrome Coronavirus (MERS-COV); these are zoonotic in origin and have been linked to fatal illness [3-5]. SARS-COV-1 and MERS-COV had a limited impact in 2003 and 2012 [6, 7]. SARS-COV-2 has caused a global pandemic and widespread testing for the virus and the resulting antibodies is considered a necessary component to restoring public health and economic stability. At the time of this writing there have been more than 5 million confirmed COVID-19 cases and over 150,000 associated deaths in the US with experts estimating that the number of deaths could exceed 300,000 by the end of 2020 [8].

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INTRODUCTION

The COVID-19 pandemic disrupted all aspects of society and demanded unpreceded initiative to address the crisis [16]. Despite dramatic improvements in health care, pandemic preparedness was one area where the world made

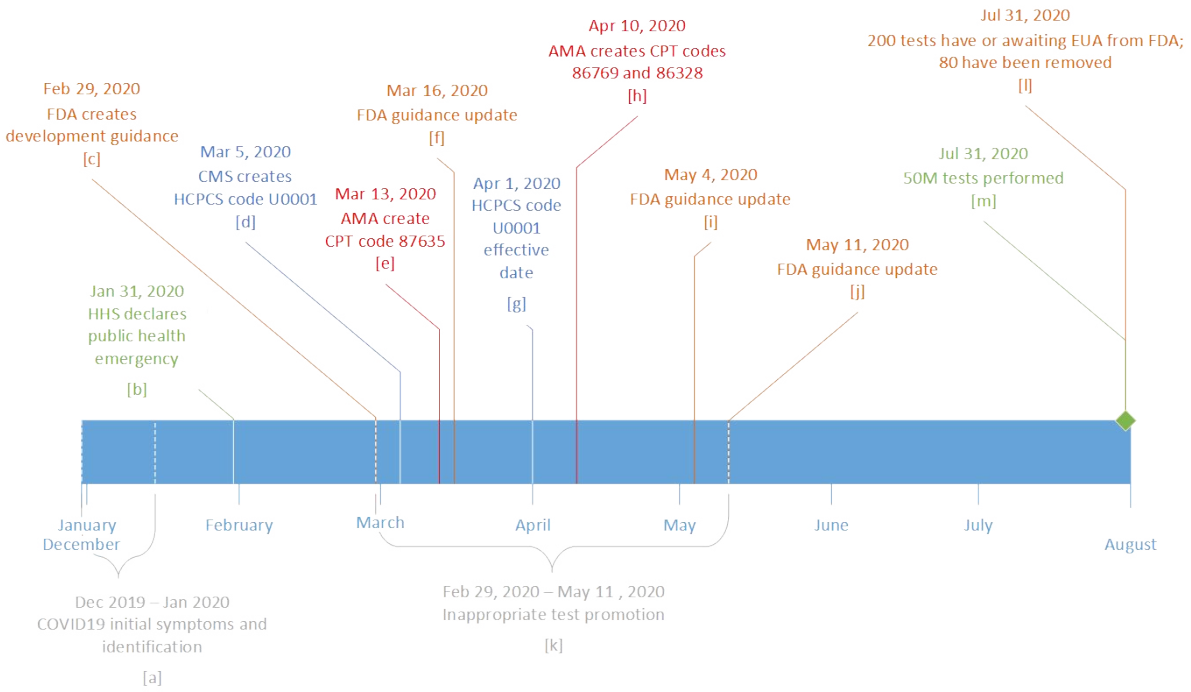

Figure 1: Timeline of COVID-19 test market. Node A, C, F, I, and J are from FDA (9). Node B is from US Department of Health Human Services (10). D and G CMS (11). Node E and H are from O'Reilly (12). Node K is from FDA (13). Node L is from FDA (14). Node M is from CDC (15).

little or no progress despite repeated calls to action [17]. The scale and impact of COVID-19 required bold leadership and rapid innovations, including the rapid scale-up of SARS-CoV-2 testing [18].

On January 31, 2020, the U.S. Department of Health & Human Services (HHS) Secretary declared a public health emergency related to the virus that causes COVID-19 [10]. This declaration justified the emergency use of in vitro diagnostics for detection and diagnosis of the SARS-CoV-2 virus. In vitro diagnostics are tests performed on human blood or tissue samples that can detect diseases or other conditions; these tests can be used to monitor a person's overall health to help cure, treat, or prevent diseases [19]. Urgency was the common theme in addressing the pandemic. Despite the global need and rapid development, lack of capacity and limited regulatory oversight led to insufficient supply and inadequate quality standards. The gap in quality and availability led to further confusion, lost resources, and possibly preventable loss of life [20]. However, this gap, was related to a significant degree, to uncertainty related to the lack of scientific knowledge of the SARS-CoV-2 virus [21]. An analysis of the early development and innovation of COVID-19 in vitro assays and lessons from the early months of this health crisis may offer suggestions to improve the response to the next phase of the pandemic.

REVIEW OF COVID-19 TEST POLICY

FDA'S EVOLVING REGULATORY FRAMEWORK

Section 564 of the Federal Food, Drug, and Cosmetic Act grants the FDA authority to allow unapproved medical devices in a public health emergency to diagnose life-threatening diseases when there are no alternatives [22]. The EUA allows the FDA to facilitate the availability and use of unapproved devices during an emergency such as COVID-19.

Following HHS' January 31 declaration, on February 29, 2020, FDA issued immediate, in effect guidance related to the development of in vitro diagnostic tests during this public health emergency [9]. The guidance was updated on March 16, May 4, and May 11, 2020. The policy bypassed the normal 510k review process whereby a premarket submission is made to FDA to demonstrate that the device is safe and effective with formal validation and clinical performance data approved by FDA prior to commercialization [9, 23].

In its initial guidance document dated March 16, 2020, the FDA provided flexibility for tests to be marketed with a simple notification to FDA with certain labeling information, but without submission of an EUA

[9]. FDA's policy was based on the urgent need to diagnose active and past COVID-19 infection and that early availability and use of these tests could help answer critical questions about the prevalence of COVID-19 infections in different communities. In addition, FDA authorized several tests under an umbrella EUA providing a streamlined approach for authorization of tests which were evaluated by the National Institutes of Health's National Cancer Institute (NIH/NCI) [9].

Subsequently, the FDA became aware that some commercial tests were being promoted inappropriately or were performing poorly based on an independent evaluation by the NIH. This necessitated greater FDA oversight on May 11, 2020, wherein the FDA updated their guidance to require commercial manufacturers to submit for an authorization to sell under an individual EUA; but the FDA did not object to continued commercial distribution and sales of tests before an EUA was authorized [13]. The approach was an attempt to balance the availability of tests and a reasonable understanding of the tests' performance. The FDA both removed poor performing tests and allowed for a greater number of new tests to be sold in the U.S. As of August 31, 2020, over 100 have been removed from distribution and almost 200 tests have an individual authorized EUA or are awaiting authorization [14]. However due to lack of resources FDA has been slow to approve individual EUAs thereby creating confusion regarding the meaning of "authorized" and appropriate performance and quality standards.

Centers for Medicare & Medicaid Services support reimbursement of COVID-19 tests

The CMS is the federal agency within the HHS that administers the Medicare program and set reimbursement guidelines. Concurrent with the FDA's policy, on February 13 and March 5, 2020, CMS announced new Healthcare Common Procedure Coding System (HCPCS) codes for healthcare providers and laboratories to test patients for SARS-CoV-2 [11]. Starting in April, laboratories performing the test could bill Medicare and other health insurers for services that occurred after February 4, 2020, using a newly created HCPCS code (U0001) [11]. Additionally, the American Medical Association (AMA) created CPT code 87635 for infectious agent detection by nucleic acid tests on March 13, 2020 as well as CPT codes 86769 and 86328 for serology tests on April 10, 2020 [12]. Following this date, laboratories performing these tests could bill Medicare for services that occurred after their respective effective dates. Commercial insurance companies were required to follow CMS' lead and all testing was fully reimbursed without any cost or co-pay to the patient [24].

CMS' policy aligned the FDA's policy regarding the development and availability of tests and the reimbursement by public and private insurers for these kits. Overnight a large and profitable $15 billion commercial market was successfully created. Below is an example of how the reimbursement works.

Example:

A clinic in Indianapolis purchased Clungene® 15 Minute Rapid COVID-19 antibody tests [14, 25]. The test successfully tested over 200 patients to correlate symptoms and infectivity and was 100% reimbursed by third party issuers. The test itself is reimbursed $45.23 under code 86328. In addition, the clinic billed for an outpatient visit under 99213 or 99203 or 99212 depending on the actual service and time provided. Given the actual cost of the test, which was on average is less than $10 [26], reimbursement was financially attractive to both diagnostic test manufacturers and healthcare providers. Below are two (2) examples of payments received from third party insurers [27].

Example 1:

Code 99213: $61.00
Code 86328: $45.23
Total: $106.23

Example 2:

Code 99203: $90.26
Code 86328: $45.23
Total: $135.49

FDA and CMS Policies: Development and availability of in vitro tests

Immediately following the alignment of the FDA and CMS's policies, hundreds of manufacturers developed a variety of test kits and notified the FDA of its intent to distribute its product on the US market and began selling tests to health care providers [28, 29]. Manufacturers simply provided a package of information to FDA which included validation, clinical performance, and instructions for use. Upon receipt, the FDA listed the manufacturers test kit on its web site with the disclaimer that the test was not FDA approved but allowed for sale based on the FDA's emergency use policy. After May 11, the FDA

listed kits as having an individual EUA or "Authorized" or "Not FDA Authorized," meaning the FDA had not yet reviewed the submission but the test was listed on the website to provide transparency regarding the notification submitted to the FDA [14]. There was also a "Setting for Use" designation which referred to a laboratory certified under Clinical Laboratory Improvement Amendments (CLIA) to perform high or medium complexity testing.

As of July 31, 2020, over 65 million COVID-19 tests have been performed and approximately 840,000 tests are being performed every day [15]. The United States is currently testing at a daily rate of 230 tests per 100,000 people (~760,000 per day), experts estimate the US needs 355 tests per 100,000 people to slow the spread of the virus, and more than 1,300 tests per 100,000 people to suppress the virus by detecting and responding to outbreaks [30].

Using the above estimates, the expectation is that the US national test/trace/track program will require 440 million per year (1.2 million per day), just to slow the spread, which is approximately 50% more than the current rate and 1.6 billion per year (4.3 million per day) to suppress the virus [30]. This translates into a market between $16 billion and $32 billion for test suppliers and up to $150 billion for lab operators. Clongene®, Abbott, Roche, Danaher, Hologic and others ramped up capacity approaching 50-million tests per year [28]. Approximately 100-million people remain under some form of stay-at-home order across the US [31], or close to one-third of the population, which is the priority group for testing.

Innovation and COVID-19 Testing

To meet the new created market, innovation flourished and manufacturers developed an amazing variety of COVID-19 in vitro tests: those that detect the genetic material of the virus to diagnose active infection and those that determine an immune response to the virus from a past infection [32].

There are two types of in vitro tests to diagnose active infection: Polymerase Chain Reaction (PCR) and Antigen. PCR tests use a molecular technique to detect genetic material from the virus. The approach amplifies a sequence of nucleic acids in order to detect tiny amounts of the virus. Because the process amplifies the sequence, the test is highly accurate, but the results can take hours or days to process. Antigen tests are designed for the rapid detection of fragments of proteins found on or within the SARS-COV-2 virus. Both are used for qualitative detection of the SARS-COV-2 virus usually from upper and lower respiratory specimens or saliva. Antigen tests have the advantage of speed; results can be provided in 15-20 minutes[i] [33]. Antigen tests are specific for the virus but not as sensitive as PCR. This means that positive results from antigen tests are highly accurate, but there is a higher chance of false negatives which do not rule out infection.

The tests that diagnose active COVID-19 infections are available in a variety of formats [34]:

- Rapid point-of-care serological tests which require only a finger prick draw of blood to detect the presence of antibodies to the virus and can be analyzed at a doctor's office within 15 minutes without any software or additional lab equipment.
- Rapid, point-of-care diagnostic tests use a mucus sample from the nose or throat but can be analyzed at the doctor's office or clinic where the sample is collected, and results may be available in minutes.
- At-home collection tests, available only by prescription from a doctor, allow the patient to collect the sample at home and send it directly to the lab for analysis.
- Saliva tests allow a patient to spit into a tube rather than get their nose or throat swabbed. Saliva tests may be more comfortable for some people and may be safer for health care workers who can be farther away during the sample collection.

In vitro serological tests determine if a person had an immune response to a COVID-19 infection. There are 3 types: rapid 15-minute Lateral Flow, ELISA and high throughput requiring specialized equipment. All are referred to as "Antibody tests" and look for antibodies to the virus, usually IgG with or without IgM, which identify individuals who have developed an adaptive immune response to the virus as part of either an active infection or a prior infection. A negative antibody test means that a person may not have had COVID-19 in the past; however, there could be a current infection and the sample for the antibody test was collected too soon to give a positive result. Antibody tests are effective after 7-12 days post onset of symptoms when sufficient time has elapsed for an immune response [35, 36].

Some diagnostic tests require a highly trained operator to manually perform the test (e.g., perform an RNA extraction step usually using specific extraction platforms and kits for PCR testing), while other tests are automated and require only limited training to perform (e.g.,

i Listed time range in the package inserts of Clungene®, Cellex, and Elecsys

15 minute rapid serological tests). Manually performed tests are authorized for use by laboratories certified to perform high-complexity tests, while automated tests are authorized for use by laboratories certified to perform moderate complexity tests at the point-of-care by facilities operating under a CLIA Certificate of Waiver [37].

Confusion in the Market

The FDA permitted a relatively unregulated COVID-19 in vitro test market to emerge. Confusion was caused by two primary issues: test accuracy and the efficacy of the claims. Test accuracy relates to the sensitivity and specificity. The first is how often and accurately a test identifies a truly positive individual as positive. This is referred to as the sensitivity of the test, with tests in the market ranging from 70% to virtually 100% [38]. Any test with a sensitivity of below 95% can be misleading due to false-negatives [29]. The second concept is how often a test identifies someone as having COVID-19, even though they really do not. This is called the specificity and again, the tests in the market vary in their levels [39]. Identifying an uninfected individual as having COVID-19 (due to low test specificity) risks not only the peace of mind of the individual (and those they are exposed to), but risks disrupting social or business activities. Any test below 95% specificity has limited utility if the prevalence in the population is low [38]. Because there is no standard reference and clinical performance data provided by manufacturers is limited, differentiating between tests from a quality perspective has been difficult.

In addition, many PCR and antigen tests require a swab from the nose, which causes a number of problems [40]. The swab might not collect a sufficient sample because COVID-19 has not replicated enough to be detected. The swab or mucus sample may be accidentally contaminated by the virus during collection or analysis. The nasal or throat swab may not be kept at the correct temperature before it can be analyzed. The chemicals used to extract the virus genetic material and make copies of the virus DNA may not work correctly. The collector may not feel comfortable inserting the swab far enough to obtain a sufficient sample [40]. Or people could simply "game the system" for personal reasons such as a fear to lose work income [41]. For self-administrated swap tests, users may not correctly follow the instructions; for example, swabbing ¼-inch into the nose instead of swabbing deep into the nasal cavity. Issues such as these have led to the FDA to publish recommendations for tests to be developed for clear and simplified use [42].

Significantly more confusion surrounded antibody testing. Serology tests play an important role in the fight against COVID-19 by helping healthcare professionals identify individuals who have developed an immune response to the SARS-CoV-2 virus. Whiles, the protective role of antibodies is unknown (so-called "immunity passports"), antibodies usually correlate with antiviral immunity, and anti–receptor-binding domain antibody levels correspond to plasma viral neutralizing activity against the virus [43]. Recent studies show that humans have a "robust" immune response to Covid-19 that may protect them from further infection. In response, an enormous diversity of antibody tests have been developed [44]. Some test for different antibodies (IgG, IgM or both), some are for high throughput laboratories which require substantial infrastructure to implement, and some use different techniques to recognize the virus. The most powerful antibodies recognize a piece of the coronavirus's spike protein, the receptor binding domain, or R.B.D. That is the part of the virus that docks onto human cells. Only antibodies that recognize the R.B.D. can neutralize the virus and prevent infection [45]. However, some tests only look for antibodies to a protein called the nucleocapsid, or N, that is bound up with the virus's genetic material. See below table (Table 1) which compares some of the antibody features.

Availability Issues

Getting access to timely results has also contributed to confusion in the market. There are reports of patients waiting weeks for results of diagnostic tests in the U.S. [48]. These delays are a result of ill-equip laboratory process for the sheer volume of incoming tests along with a reliance on tests with slow turnaround. For diagnostic tests that require a laboratory to determine the result, waiting two or more days to confirm infection may lead to additional infections via suboptimal quarantine practices or wasted time and income [49].

By way of comparison with other countries, a greater number of available tests options does not correlate with better care. South Korea has successfully contained the virus and offers 23 approved test options [50]. The European Union, with a less onerous CE mark framework than the US FDA, have 466 testing options and many EU countries have struggled to contain the virus [51, 52]. The US has 68 approved tests and has approximately 150 unapproved tests that are allowed to be commercialized at this time [53].

Hoping to improve availability, on July 29, 2020, FDA published guidance to encourage test developers to create more accessible COVID-19 tests [42]. FDA is recommending that tests be simple enough for at-home and over-the-counter use in non-lab settings. One EUA under this new guideline was recently provided to Yale

Table 1

Test	Receptor binding	Specificity	IgG Sensitivity post 14 days	1:1 diluent to test?	Rapid test?
Clungene®	Spike and Nucleocapsid	96.5% (a)	100%	Yes	Yes, 15 minutes
Abbott Architect SARS-CoV-2 IgG	Nucleocapsid	99.6	100%	High throughput CMIA only	No
Cellex qSARS-CoV-2 IgG/IgM Rapid Test	Spike and Nucleocapsid	96%	93.8%	No	Yes, 15 minutes
Roche Elecsys Anti-SARS-CoV-2	Nucleocapsid	100%	99.8	No	High throughput CMIA only

Note: See Instructions for Use listed on FDA website [46].

Clungene® specificity result from interim clinical study results (100% specificity at 95% CI (88.4%, 100%) and sensitivity results from data submitted to FDA [47].

School of Public Health's "SalivaDirect" diagnostic test [54]. This test checks for the SARS-CoV-2 virus in saliva, which does not need the use of swabs; swabs have been the focal point of shortages, patient discomfort, and testing errors. By setting development standards and clearly communicating the public health needs, FDA is encouraging and directing innovative solutions to alleviate testing availability.

DISCUSSION AND CONCLUSION

An assessment of FDA's policy during the first eight (8) months of the crisis reveals several key lessons learned regarding product development and innovation during a public health crisis. The FDA's policy was successful if the measure of success is the number and quantity of tests. Within 6 months, manufacturers were able to develop hundreds of tests and a test capacity exceeding 500 million tests. However, the tradeoff was the lack of standards by which health care practitioners could evaluate different tests and the need for the FDA to remove more than 100 tests from the market for poor performance. There were also many other uncertainties, including the logistics of deployment; the ease and comfort of sample collection, scalability, turnaround time, and cost of test kits [55]. There are societal benefits to casting a wide net with faster, less accurate tests, but this has caused confusion on a societal and personal level.

Antigen tests provide a low-cost way to do a great deal of tests which is better than no testing, and it supports the goal of being able to isolate and quarantine infected people. Widespread, quick testing is the foundation of any pandemic response but an area where the United States has consistently fallen short in comparison to other countries (See Figure 2 below) [56].

In order to ramp up testing to a level needed to stop the spread of the virus, experts are increasingly recommending a strategy that casts a wider net with widespread adoption of faster, but more accurate tests [57]. But increased testing comes at a cost. As cases spike, demand has overwhelmed laboratories, and shortages in the supply chain meant many Americans had to wait days — or even weeks — for results. The delays substantially reduce the value of testing. Results are needed within 24 to 48 hours to effectively quarantine and contact trace. In the United States, turnaround times are often stretching three to five days, or more [58-60].

Overall, FDA, with support from CMS, has provided a regulatory and financial innovative framework for successfully developing innovative tests to address the pandemic. Overnight, different tests with different capabilities were provided to government and healthcare providers. In some ways, testing in America is a success story. Within six months, the U.S. does more COVID-19 testing than any other country but also has the greatest number of cases (see Figure 2).

Yet the speed and accuracy of the testing vary widely; results often are too slow to be meaningful and those tested could be unwitting carriers of the disease while waiting they wait for results. Quality standards and clear guidance on test performance claims had made implementation difficult.

Moving forward, there are four recommendations to improve COVID-19 in vitro testing response. First, all tests should be evaluated by FDA within 30 days after submission. Second, all tests should be evaluated using a common reference standard and all performance claims should be provided in the Instructions for Use against the common standard. Third, widespread and large epidemiological studies and testing for certain high risk groups should be undertaken using both diagnostic and

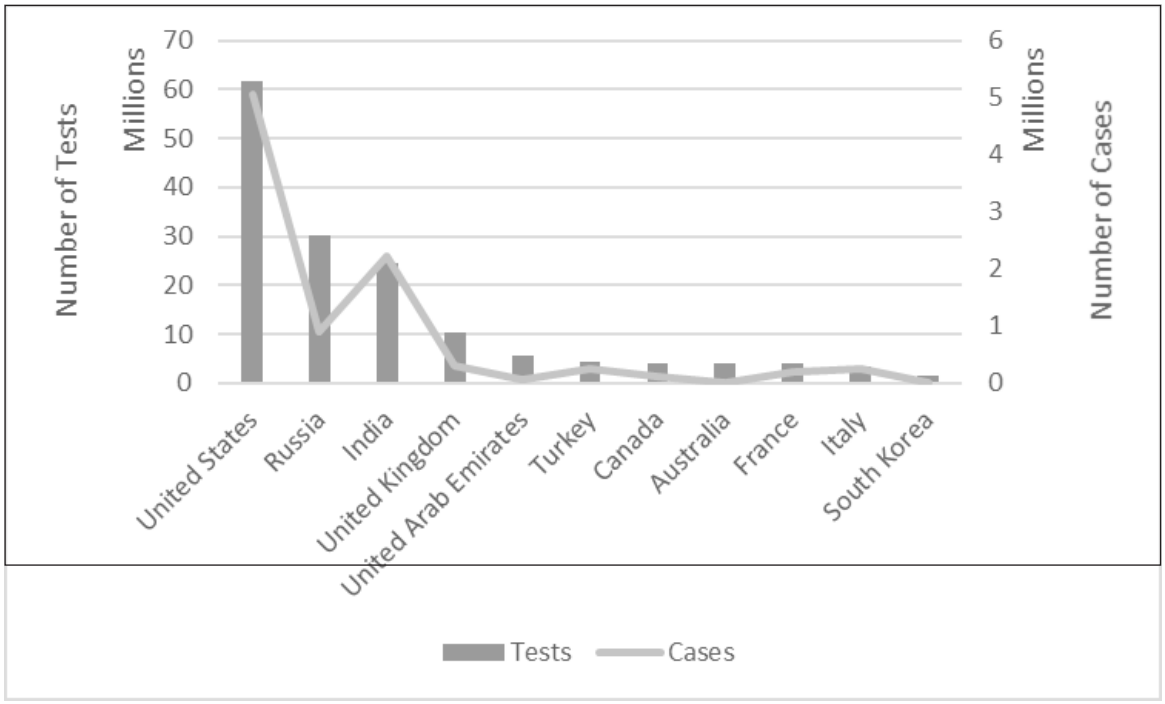

Figure 2: Top ten countries for with the most COVID-19 tests. South Korea is included for a comparison with a country that did a good job of containing the virus. Bars represent total tests. Lines represent total cases. Dataset source [56] → https://ourworldindata.org/coronavirus

serological testing throughout the US as recommended by the Infectious Disease Society of America [61, 62]. Fourth, a nationally funded testing technology accelerator should be established immediately with the goal of dramatically improving test performance.

Innovation in the time of the COVID-19 public health crisis has been demonstrated but it has not been sufficient. FDA has provided a flexible regulatory framework for the rapid development of in vitro diagnostic tests and CMS has provided the necessary financial incentive. But far more innovation is needed, and greater resources are required from both government and industry to make an effective testing policy a reality. The health and economic stakes are too high to do otherwise.

DISCLOSURE

Christopher C. Lamb, PhD, has worked with the manufacturers of SARS-CoV-2 tests for Emergency Use Authorization submissions to the US FDA.

FUNDING

No external funding was received for this work.

ACKNOWLEDGEMENTS

The author acknowledges Ryan Dagenais for assistance with literature review and editorial support with the manuscript; his efforts were funded by BioSolutions Services LLC.

REFERENCES

1. Yuen, K.-S., Ye, Z.-W., Fung, S.-Y., Chan, C.-P. & Jin, D.-Y. (2020). SARS-CoV-2 and COVID-19: The most important research questions. *Cell & bioscience*. 10(1), 1–5.
2. Schoeman, D. & Fielding, B. C. (2019). Coronavirus envelope protein: current knowledge. *Virology journal*. 16(1), 1–22.
3. Peeri, N. C., Shrestha, N., Rahman, M. S., Zaki, R., Tan, Z., Bibi, S., et al. (2020). The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *International journal of epidemiology*.
4. Zumla, A., Hui, D. S. & Perlman, S. (2015). Middle East respiratory syndrome. *The Lancet*. 386(9997), 995–1007.

5. Chen, Y., Liu, Q. & Guo, D. (2020). Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of medical virology*. 92(4), 418–23.
6. Hilgenfeld, R. & Peiris, M. (2013). From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antiviral research*. 100(1), 286–95.
7. Rha, B., Rudd, J., Feikin, D., Watson, J., Curns, A. T., Swerdlow, D. L., et al. (2015). Update on the epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, and guidance for the public, clinicians, and public health authorities-January 2015. *MMWR Morbidity and mortality weekly report*. 64(3), 61.
8. Hawkins, D. & Iati, M. (2020). Birx says U.S. has entered a 'new phase' of pandemic as cases, deaths rise.
9. FDA. Policy for coronavirus disease-2019 tests during the public health emergency (revised) 2020 [updated May 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised.
10. US Department of Health Human Services. Secretary Azar declares public health emergency for United States for 2019 novel coronavirus. 2020 Jan 31. 2020.
11. CMS. CMS Develops Additional Code for Coronavirus Lab Tests: Centers for Medicare and Medicaid Services,; 2020 [Available from: https://www.cms.gov/newsroom/press-releases/cms-develops-additional-code-coronavirus-lab-tests.
12. O'Reilly, K. (2020). New CPT code for COVID-19 testing: What you should know: AMA; [Available from: https://www.ama-assn.org/delivering-care/public-health/new-cpt-code-covid-19-testing-what-you-should-know#:~:text=But%20those%20are%20for%20nucleic,pan%2Dcoronavirus%20types%20or%20subtypes.
13. FDA. Coronavirus (COVID-19) Update: Daily Roundup May 11, 2020: FDA; 2020 [Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-may-11-2020.
14. FDA. FAQs on Testing for SARS-CoV-2: FDA; 2020 [updated 7/30/2020. Available from: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-testing-sars-cov-2.
15. CDC. Testing Data in the US: Centers for Disease Control and Prevention; 2020 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/testing-in-us.html.
16. Woolliscroft, J. O. (2020). Innovation in response to the COVID-19 pandemic crisis. *Academic Medicine*.
17. Gates, B. (2018). Innovation for pandemics. *New England Journal of Medicine*. 378(22), 2057–60.
18. Guest, J. L., del Rio, C. & Sanchez, T. (2020). The three steps needed to end the COVID-19 pandemic: bold public health leadership, rapid innovations, and courageous political will. *JMIR Public health and surveillance*. 6(2), e19043.
19. FDA. In Vitro Diagnostics EUAs: FDA; 2020 [Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas.
20. Sebenius, I. & Sebenius, J. K. (2020). How many needless Covid-19 deaths were caused by delays in responding? Most of them: STAT; [Available from: https://www.statnews.com/2020/06/19/faster-response-prevented-most-us-covid-19-deaths/.
21. Djalante, R., Shaw, R. & DeWit, A. (2020). Building resilience against biological hazards and pandemics: COVID-19 and its implications for the Sendai Framework. *Progress in Disaster Science*. 100080.
22. FDA. Emergency Use Authorization: FDA; 2020 [Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#:~:text=Under%20section%20564%20of%20the,caused%20by%20CBRN%20threat%20agents.
23. FDA. Updated Letter to Industry on COVID-19 2020 [Available from: https://www.fda.gov/media/136696/download.
24. McGuireWoods. Recent Changes for Medicare and Commercial Insurers to Improve Access to COVID-19 Testing 2020 [Available from: https://www.mcguirewoods.com/client-resources/Alerts/2020/4/recent-changes-medicare-commercial-insurers-improve-access-covid-19-testing.
25. FDA. Clungene SARS-COV-2 VIRUS (COVID-19) IgG/IgM Rapid Test Cassette: FDA; 2020 [Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/rl.cfm?lid=660403&lpcd=QKO.
26. Haseltine, W. A. (2020). Tests For COVID-19 Are Expensive, But They Don't Have To Be: Forbes; [Available from: https://www.forbes.com/sites/williamhaseltine/2020/04/08/pricing-and-profiteering-from-covid-19-tests/#184769041ccb.
27. Proven Pharma LLC. *Indianapolis dataset*. 2020.
28. Herper, M. (2020). Test makers are moving fast, but the coronavirus may be moving faster: STAT; [Available

from: https://www.statnews.com/2020/03/31/test-makers-are-moving-fast-but-the-coronavirus-may-be-moving-faster/.

29. Farley, P. & Sanders, R. (2020). Testing the Tests: COVID-19 Antibody Assays Scrutinized for Accuracy by UCSF, UC Berkeley Researchers: University of California San Francisco; [Available from: https://www.ucsf.edu/news/2020/04/417276/testing-tests-covid-19-antibody-assays-scrutinized-accuracy-ucsf-uc-berkeley.
30. HGHI. Daily COVID-19 Tests vs. Tracing Targets [as of 6/23/2020]: Harvard Global Health Institute; 2020 [8/9/2020]. Available from: https://globalepidemics.org/july-6-2020-state-testing-targets/.
31. US Department of Transportation. Daily Travel during the COVID-19 Pandemic: US Department of Transportation; 2020 [Available from: https://www.bts.gov/browse-statistical-products-and-data/trips-distance/daily-travel-during-covid-19-pandemic.
32. FDA. Coronavirus Testing Basics 2020 [Available from: https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics.
33. FDA. Coronavirus (COVID-19) Update: FDA Authorizes First Antigen Test to Help in the Rapid Detection of the Virus that Causes COVID-19 in Patients 2020 [Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes.
34. CDC. Test for Current Infection: Centers for Disease Control and Prevention; 2020 [updated July 23, 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/testing/diagnostic-testing.html.
35. Osher, G., Lamb, C. C., Ibarra, Y. & Erickson-Samson, D. (2020). Observational Study of SARS-CoV-2 Antibody Immune Response in a Cohort of Patients at a North Suburban Chicago, Illinois Physician's Practice. *LymphoSign Journal*.
36. Ransegnola, B., Jin, D., Lamb, C. C., Shaz, B. H., Hillyer, C. D. & Luchsinger, L. L. (2020). COVID 19 Antibody Detection using Lateral Flow Assay Tests in a Cohort of Convalescent Plasma Donors. *BMC Research Notes*.
37. CMS. How to obtain a CLIA Certificate of Waiver: CMS; 2019 [Available from: https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/howobtaincertificateofwaiver.pdf.
38. Waller, J. V., Kaur, P., Tucker, A., Lin, K. K., Diaz, M. J., Henry, T. S., et al. (2020). Diagnostic Tools for Coronavirus Disease (COVID-19): Comparing CT and RT-PCR Viral Nucleic Acid Testing. *American Journal of Roentgenology*. 1–5.
39. Oladimeji, P. & Pickford, J. (2020). Letter of concern re:"Comparison of seven commercial RT-PCR Diagnostic kits for COVID-19" van Kasteren et al, Clinical Journal of Virology: https://doi. org/10.1016/j. jcv. 2020.104412. *Journal of Clinical Virology*.
40. DeMarco, C. (2020). 11 things to know about COVID-19 testing: MD Anderson Cancer Center; [Available from: https://www.mdanderson.org/cancerwise/is-covid-19-coronavirus-testing-accurate-and-9-more-things-to-know-about-covid-19-nasal-swab-testing.h00-159381945.html.
41. Pradhan, R. (2020). As Problems Grow With Abbott's Fast COVID Test, FDA Standards Are Under Fire: Kaiser Health News; [Available from: https://khn.org/news/abbott-rapid-test-problems-grow-fda-standards-on-covid-tests-under-fire/.
42. FDA. Coronavirus (COVID-19) Update: FDA Posts New Template for At-Home and Over-the-Counter Diagnostic Tests for Use in Non-Lab Settings, Such as Homes, Offices or Schools 2020 [updated 7/29/2020. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-posts-new-template-home-and-over-counter-diagnostic-tests-use-non.
43. Ibarrondo, F. J., Fulcher, J. A., Goodman-Meza, D., Elliott, J., Hofmann, C., Hausner, M. A., et al. (2020). Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild Covid-19. *New England Journal of Medicine*.
44. Rodda, L. B., Netland, J., Shehata, L., Pruner, K. B., Morawski, P. M., Thouvenel, C., et al. (2020). Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. medRxiv. 2020.08.11.20171843.
45. Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z., et al. (2020). Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerging microbes & infections*. 9(1), 382–5.
46. FDA. EUA Authorized Serology Test Performance 2020 [Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance.
47. Haddad, F. IgG/IgM Antibody Test in Patients Who Have Tested Negative or Positive for COVID-19 With the Standard Method of COVID19 Testing. ClinicalTrials.gov: U.S. National Library of Medicine; 2020 [updated 7/27/2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04402814?cond=clungene&draw=2&rank=1.
48. Krouse, S. & Terlep, S. (2020). Why Is It Hard to Get a Rapid Covid-19 Test? The Machines Are in Short Supply: The Wall Street Journal; [Available from: https://www.

wsj.com/articles/rapid-response-covid-19-test-makers-face-outsize-demand-11597231427?mod=hp_lead_pos6.

49. Billingsley PhD A. (2020). The Latest in Coronavirus (COVID-19) Testing Methods and Availability: GoodRx; [Available from: https://www.goodrx.com/blog/coronavirus-covid-19-testing-updates-methods-cost-availability/.

50. FIND. SARS-COV-2 Diagnostic Pipeline: South Korea: Foundation for Innovative New Diagnostics; 2020 [Available from: https://www.finddx.org/covid-19/pipeline/?avance=all&type=all&test_target=all&status=Korea+MFDS+EUA&section=show-all&action=default.

51. FIND. SARS-COV-2 Diagnostic Pipeline: Europe: Foundation for Innovative New Diagnostics; 2020 [Available from: https://www.finddx.org/covid-19/pipeline/?avance=all&type=all&test_target=all&status=CE-IVD&section=show-all&action=default.

52. Conley, D. (2015). Two Paths for Medical Device Approval: FDA vs CE. *Health Management*. 15(2).

53. FIND. SARS-COV-2 Diagnostic Pipeline: United States: Foundation for Innovative New Diagnostics; 2020 [Available from: https://www.finddx.org/covid-19/pipeline/?avance=all&type=all&test_target=all&status=US+FDA&section=show-all&action=default.

54. FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization to Yale School of Public Health for SalivaDirect, Which Uses a New Method of Saliva Sample Processing: FDA; 2020 [updated 8/15/2020. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-yale-school-public-health.

55. Paltiel, A. D., Zheng, A. & Walensky, R. P. (2020). Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. *JAMA Network Open*. 3(7), e2016818-e.

56. Ritchie, H., Ortiz-Ospina, E., Beltekian, D., Mathieu, E., Hasell, J., Macdonald, B., et al. (2020). Statistics and Research: Coronavirus Pandemic (COVID-19); [updated 8/10/2020. Available from: https://ourworldindata.org/coronavirus.

57. Allen, D., Krein, J., Sitaraman, G. & Glen Welyl, E. (2020). National Covid-19 Testing Action Plan: Pragmatic steps to reopen our workplaces and our communities: The Rockefeller Foundation.

58. Volz, M. & PGalewitz, P. (2020). As Long Waits for Results Render COVID Tests 'Useless,' States Seek Workarounds: Kaiser Health News; [Available from: https://khn.org/news/states-search-for-ways-to-deal-with-covid-19-testing-backlogs/.

59. Esbin, M. N., Whitney, O. N., Chong, S., Maurer, A., Darzacq, X. & Tjian, R. Overcoming the bottleneck to widespread testing: A rapid review of nucleic acid testing approaches for COVID-19 detection. *RNA*. 2020:rna.076232.120.

60. Behnam, M., Dey, A., Gambell, T. & Talwar, V. COVID-19: Overcoming supply shortages for diagnostic testing [Available from: https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/covid-19-overcoming-supply-shortages-for-diagnostic-testing#.

61. Hanson, K. E., Caliendo, A. M., Arias, C. A., Englund, J. A., Hayden, M. K., Lee, M. J., et al. (2020) Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Serologic Testing: IDSA; [Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/.

62. Bhimraj, A., Morgan, R. L., Shumaker, A. H., Lavergne, V., Baden, L., Cheng, V. C.-C., et al. (2020). Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clinical Infectious Diseases*.

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The *Journal of Commercial Biotechnology* is published quarterly in Washington, DC by thinkBiotech LLC.

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Print ISSN: 1462-8732
Online ISSN: 1478-565X

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