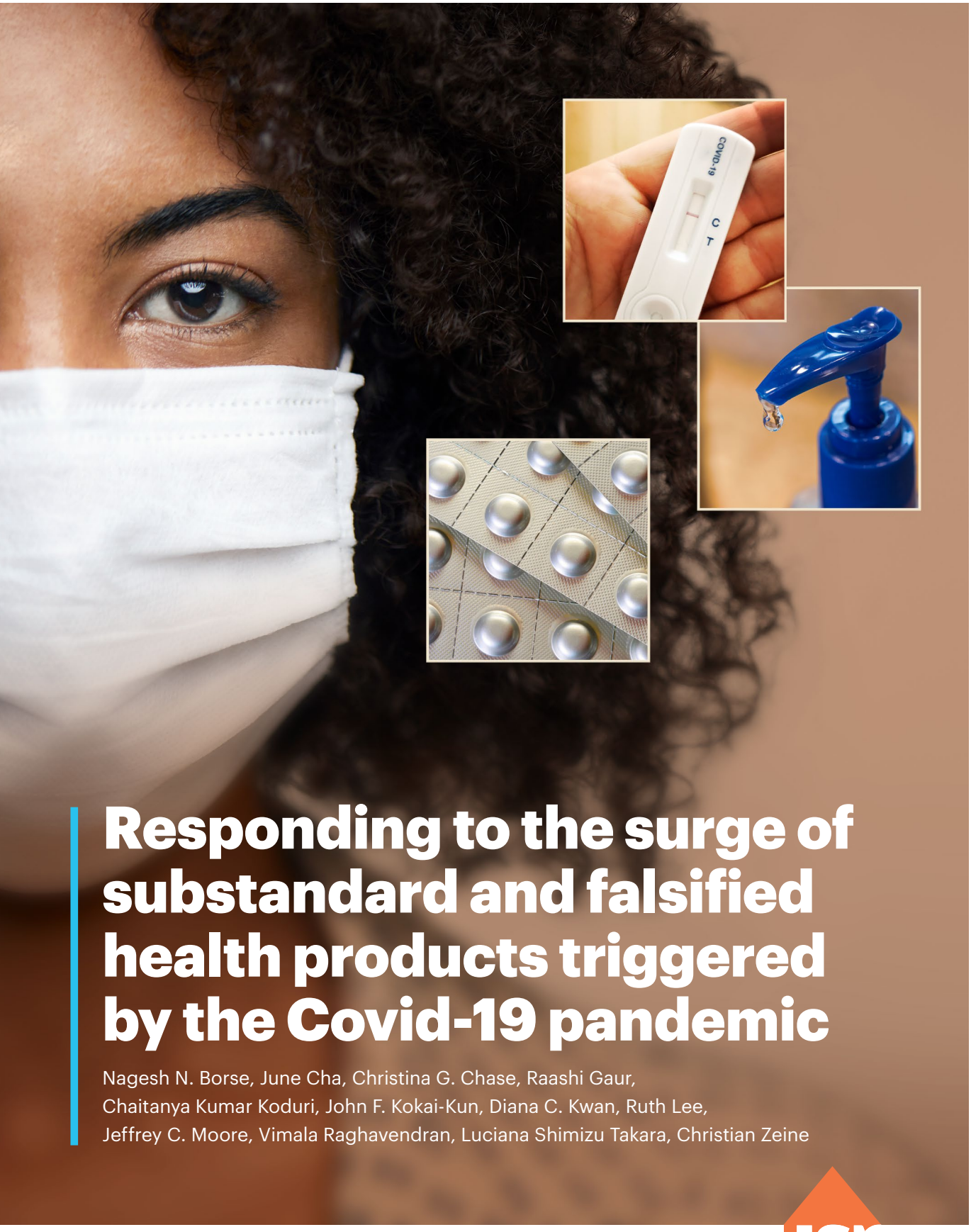


Responding to the surge of substandard and falsified health products triggered by the Covid-19 pandemic

Nagesh N. Borse, June Cha, Christina G. Chase, Raashi Gaur,
Chaitanya Kumar Koduri, John F. Kokai-Kun, Diana C. Kwan, Ruth Lee,
Jeffrey C. Moore, Vimala Raghavendran, Luciana Shimizu Takara, Christian Zeine

May 2021

Introduction

Substandard and falsified medical products such as vaccines and medicines are a serious and growing global health issue[1]. Other health products such as diagnostic kits and infection preventatives, including but not limited to masks and hand sanitizers, are also found on the market in substandard and falsified versions, as discussed below. In this article, the authors refer to all of these products as substandard and falsified health products (SFHP).*

COVID-19, like previous pandemics, has increased the vulnerability of global supply chains to SFHP. This paper explores the basics of SFHP, reviews what we have learned from past pandemics, and offers a perspective on existing and needed tools to protect health products, and the people who use them, from the threat of SFHP.

* The authors are aware that the term substandard and falsified medical products or its abbreviation SFMP is also commonly used. However, to include other health products subject to being substandard or falsified it was decided to use the more inclusive term SFHP.

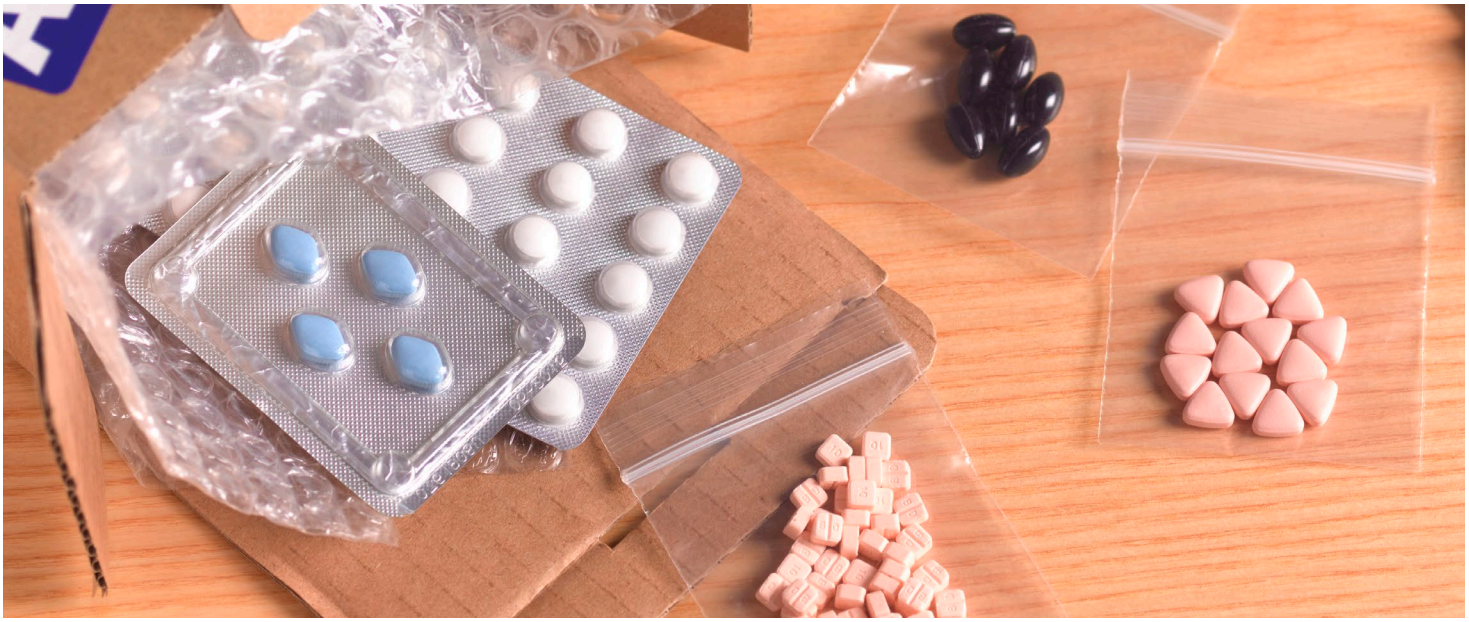
Background on the problem of substandard and falsified health products

Overview

The problem of SFHP in general, and of substandard or falsified (SF) medicines and vaccines in particular, is a serious public health concern[1-4]. The World Health Organization (WHO) defines substandard medical products as "authorized medical products that fail to meet quality standards or specifications, or both." Substandard products may result from inadequate or improper manufacturing, shipping, or storage, or they may have expired. Falsified medical products are defined as "products that deliberately / fraudulently misrepresent identity, composition, or source"[5-6].

The WHO estimates that 10.5% of medicines worldwide are SF, and the percentages are typically higher in low- and middle-income countries (LMICs)[1,7]. A systematic review found that 13.6% of essential medicines tested in LMICs failed quality criteria. The highest SF prevalence was in Africa, where 18.7% of samples were unsatisfactory, while the prevalence was 13.7% in Asia and 14.4% in other regions[7].

SF medicines can be found in illegal street markets, pharmacies, clinics, and hospitals, as well as on unregulated websites[6]. Antimalarials and antibiotics are among the most commonly reported SF medicines but all types of drugs can be substandard or falsified. Further studies are needed to better understand the quality profile of other essential medicines[6,7].



Adverse health outcomes caused by SF medicines include illness and death from treatment failure or adverse drug reactions; antimicrobial resistance; and loss of public confidence in medicines, healthcare providers, and drug manufacturer[2,3]. The harm also extends beyond health consequences to socioeconomic impacts such as increased costs for patients, families, and governments; worsening poverty; and reduced economic productivity[2,3,6]. Furthermore, SF medicines are a major threat to global health security, hampering efforts to meet the United Nations Sustainable Development Goal 3.8 of achieving universal access to safe and effective essential medicines.

SF products often emerge in the wake of shortages, which can lead to panic buying and hoarding by consumers as well as sharp increases in prices. All of these factors are interrelated and they create market opportunities for unscrupulous producers, distributors, and sellers[8,9]. During pandemics, the prevalence of SF products rises even further due to impacts on manufacturing capacity, raw material supply, consumers' uncertainty about treatment effectiveness, and their perception that they need to find effective alternative therapies urgently. Unfounded claims and promotion of SF products through the internet and social networks can interact with the public's lack of awareness about risks, thereby driving up sales of these products[10].

Learnings about SF medicines and vaccines from past pandemics and epidemics

Tamiflu

In the early 2000s, rising influenza rates and a possible avian flu (H5N1) pandemic led to high demand for oseltamivir (Tamiflu). Countries and individuals were actively stockpiling the antiviral, which was approved by the U.S. Food and Drug Administration (FDA) in 1999 for prevention and early treatment of influenza and was also used off-label for avian flu. There was no generic version of Tamiflu, and the sole manufacturer, Roche, did not produce enough to meet the demand. Criminal elements started to produce falsified Tamiflu that contained no active ingredient and provided no therapeutic effect[11].

Roche addressed the problem by increasing production to further meet the demands of the population. Roche also provided guidance to consumers on how to recognize falsified Tamiflu. The U.S. Centers for Disease Control responded by developing a toolbox of analytical methods (colorimetric and liquid chromatographic) that could be used by customs agencies and medicine regulatory authorities to rapidly detect falsified oseltamivir. The analytical methods were simple and affordable, which was especially valuable for developing countries with limited resources[12].

The Tamiflu example illustrates that a supply/demand imbalance presents an opportunity for bad actors to introduce SF medicines. It also shows that a multi-pronged effort is critical for informing and educating consumers and medicine regulatory authorities on how to distinguish false from genuine products.

Selected incidents involving SF vaccines

In 1995, during a meningitis epidemic, ~60,000 Nigerians were injected with water disguised as meningitis vaccine, causing ~2,500 to 3,000 excess deaths[13]. In China, substandard hepatitis B and rabies vaccines killed or sickened ~100 infants in March 2010[14]. In these incidents, the SF vaccines failed to stimulate immunity in the recipients, and the community as a whole was also harmed because an SF vaccine does not achieve progress toward herd immunity. This scenario opens the door for outbreaks on a regional scale.

SF vaccines can cause another type of harm by eroding the public's trust in vaccination programs. For instance, a Chinese vaccine maker was found to have fabricated production and inspection records after arbitrarily changing process parameters and equipment during its production of human rabies vaccines in 2018. The same company produced substandard diphtheria, pertussis, and tetanus (DPT) vaccines that were administered to 215,184 Chinese children; a total of 400,520 substandard DPT vaccines were sold domestically[15]. A huge crisis in the public's vaccine confidence resulted, seriously threatening the future success of vaccination programs.

Vaccine hesitancy has been linked to the resurgence of nearly eradicated diseases such as measles in the United States. A broad range of factors are linked to vaccine hesitancy including lack of active community engagement in vaccination programs, their coincidental temporal relationships to adverse health outcomes, unfamiliarity with vaccine-preventable diseases, and lack of trust in corporations and public health agencies[16]. The WHO has identified vaccine hesitancy as one of the largest health threats of 2019[1].

Not surprisingly, given the severe gap in demand and supply of vaccines, it has been predicted that falsified, diverted, and substandard (especially degraded) vaccines are highly likely to become a worsening global public health problem. An overview of vaccine quality related incidents to COVID-19 includes early reports and warnings about fake versions raise similar concerns[18].

Global landscape for substandard and falsified health products during COVID-19

United States

Since the declaration of a public health emergency due to COVID-19 in February 2020, the U.S. government has been vigilant in its efforts to combat fraudulent medical products. The FDA has established a COVID-19 Fraud Task Force, partnering with other federal regulatory and law enforcement agencies including the Federal Trade Commission (FTC), U.S. Department of Justice, and U.S. Department of Homeland Security to coordinate investigations, enforcement activities, and public information sharing.

As of February 15, 2021, FDA has issued 145 warning letters, some jointly with FTC, to actors involved in making false drug claims about unapproved COVID-19-related use[19]. These warning letters request responses within 48 hours of receipt, which is an accelerated timeline compared to the usual 15 business days. FDA has also issued safety alerts warning the public against the use of certain unapproved, potentially dangerous products. For example, FDA recently issued alerts to health care professionals and compounders regarding potential health risks from compounded remdesivir products[20].

FDA also placed all alcohol-based hand sanitizers from Mexico on a country-wide import alert to stop any products at risk of contamination from entering the U.S. market[21]. In parallel, the U.S. Department of Homeland Security is investigating a counterfeit N95 mask operation[22]. The inter-agency collaborations are expected to continue to stop the production and sale of products that fraudulently claim to diagnose, cure, mitigate, treat, or prevent COVID-19[23]. These collaborations may also move on to more complex areas to ensure the quality of approved products.

Europe

SFHP are also a concern in Europe. SF versions of COVID-19 vaccines are assumed to be on the European market already, as warned in early 2021 by Germany's international broadcaster Deutsche Welle[24] and in December 2020 by Europol in an Early Warning Notification[25]. Between March and September 2020, Europol coordinated Operation Shield, a global effort to target trafficking of counterfeit and misused medicines and doping substances. The operation involved law enforcement authorities from 27 countries (19 EU Member States and 8 third-party countries), the European Anti-Fraud Office (OLAF), the Pharmaceutical Security Institute, and the private sector. During the operation, law enforcement officers dismantled 25 criminal groups, arrested nearly 700 suspects, and seized substantial amounts of drugs in many therapeutic areas. The following falsified products related to COVID-19 were seized: Almost 33 million face masks, tests, and diagnostic kits; 8 tons of raw materials, chemicals, and antivirals; and 70,000 liters of sanitizers[26].

India

The National Medicine Regulatory Authority of India, CDSCO (Central Drugs Standards Control Organization), conducts a monthly analysis of samples collected across the country. From January to December 2020, 39 instances of substandard hand sanitizers containing methanol were reported [27]. There were also reports of substandard personal protective equipment (PPE) kits, including N95 masks, being supplied to frontline hospital workers[28].

Substandard remdesivir was withdrawn from the Indian market in September 2020[29]. However, there is further risk of substandard remdesivir entering the market because pharmacists' stock will be expiring soon and will not be taken back by the manufacturers[30,31].

During 2020, there were also multiple reports of substandard dexamethasone:

- Dexamethasone, along with 24 other medicines, was declared substandard by the Indian national regulator due to the presence of free dexamethasone, flawed assay of the active pharmaceutical ingredient (API), and sterility issues[32].
- In July 2020, Indian Intelligence provided information on a shipment being delivered to Lagos containing a significant amount of counterfeit dexamethasone.[33]
- In March 2020, a man was arrested while smuggling the product from Indonesia into Singapore, and a woman experienced chest discomfort after taking an herbal product containing dexamethasone that was bought by a friend in Malaysia[34].
- A systematic review reported that the prevalence of poor-quality dexamethasone was 3.14% –32.2% in LMICs. The reasons included an inadequate amount of API and presence of free dexamethasone in the samples[35].

Southeast Asia

The region of Southeast Asia is purported to be a hub for falsified medicines [36]. During the 2019 ASEAN (The Association of Southeast Asian Nations) Health Ministers Meeting[37], a Joint Statement was made to support the ASEAN Action Plan for combatting SF medicines. The Plan calls for strengthening national regulatory mechanisms and collaborating to prevent, detect, and eliminate SF medical products within countries and across the region. A comprehensive United Nations study about transnational organized crime found that production of counterfeit goods and falsified medicines is a high-profit endeavor of criminal syndicates in Southeast Asia[38].

Latin America

In Latin America, the coronavirus pandemic has created an opportunity for the proliferation of SF medical products. SF and unregistered medical products were already a highly prevalent public health problem in the region before COVID-19. It appears that the pandemic may have worsened the problem, but there is currently a lack of robust, compiled data to document this.

Data on SFHP are available for certain countries. In Costa Rica, Interpol's Operation Pangea XIII seized more than 11,000 units of illegal products, including drugs and false medicinal products worth almost US $125,000[39]. Health authorities in Peru seized 4 tons of falsified medicines during the COVID-19 pandemic[40]. In Mexico, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) issued a health alert about falsification and illegal marketing of the drugs ivermectin, ivermin, and hydroxychloroquine, known for their unproven claims of efficacy in preventing or combating COVID-19[41,42].

In Brazil, the National Health Surveillance Agency (ANVISA) warned that in the first five months of 2020, 16 cases of counterfeiting were identified, a number four times higher than in all of 2019[43]. ANVISA also launched an analytical panel which allows visualizing products / manufactures and measures adopted by ANVISA with respect to irregular products. Regarding the diagnostic tests for COVID-19 infection, about 40% were considered unsatisfactory according to one report [44].

Tools needed to protect vulnerable health products from substandard and falsified risk

Investments are needed to support rapid development of tools and capability-building resources that can guard the most vulnerable medicines from the threat of becoming substandard or falsified. Considering the rapidly changing landscape of health products, these tools need to be developed using an approach that allows for evolution.

Tools to ensure the quality of vaccines

The COVID-19 pandemic requires a global response to allow the world to reach a post-pandemic resumption of daily life. Part of this global response is the development and deployment of effective vaccines to provide protection from

SARS-CoV-2 infection and COVID-19. Unprecedented efforts have resulted in the rapid development and Emergency Use Authorization (EUA) of several vaccines for COVID-19, with many more in earlier stages of development[45]. This worldwide rollout of vaccines will require the combined efforts of innovators, global health organizations, local manufacturers, and regulators.

Part of the global effort towards vaccine deployment includes decentralized manufacturing, in some cases with fill/finish of vaccines in smaller local manufacturing facilities. Further, local regulatory authorities will need to identify gaps in their systems and capabilities for testing and release of vaccines in their individual countries[46]. National control laboratories and quality control laboratories at local manufacturers and in various countries will have varying requirements for testing. Development and validation of the analytical assays for this testing can be resource intensive, time consuming, and expensive. However, USP has a variety of resources available, in the form of general chapters and scientific expertise, to assist and support these types of laboratories in the development and validation of various assays required to test and release COVID-19 vaccines.

Analytical assays for testing and release of vaccines can be organized into three general categories (**Table 1**): 1) general or compendial assays (e.g., appearance), 2) platform-specific assays (e.g., product- and process-related impurities), and 3) product-specific assays (e.g., identity and potency). *The U.S. Pharmacopeia–National Formulary* (*USP–NF*) has resources available, such as its general chapters, to support these various types of assays. Identity assays may be particularly important to help ensure that falsified vaccines do not enter the supply chain. Some of the general chapters (those numbered <1000) can provide step-by-step methods for performing the assays, while other chapters (those >1000) provide useful information and best practices to support various assays. USP is working to make these resources available to the global community to facilitate the worldwide response to COVID-19.

These quality-assured vaccines must then be managed through a secure supply chain and handled correctly at each point of the distribution process. USP's COVID-19 Vaccine Handling Toolkit: Operational Considerations for Healthcare Practitioners[47] provides strategies for the handling and administration of the U.S. FDA–authorized COVID-19 vaccines, and the toolkit can be tailored to local requirements and conditions. Resources such as this toolkit help to increase efficiencies in mass vaccination efforts and also minimize waste of these precious vaccines, which can be rendered substandard and ineffective if there are deviations from quality practices during transportation, storage, or handling.

Category of Assay	Attribute	Examples of *USP–NF* General Chapters
General vaccine chapters	General	<1> <1235> <1239> <1047>
General/compendial assays	Appearance	<1> <631> <788> <1787> <1790>
	Concentration	<507>
	pH and osmolality	<791> <785>
	Sterility	<71>
	Endotoxin	<85>
Platform-specific assays	Purity	<1054> <1056> <621>
	Critical excipients	<1074>
Vaccine-specific assays	Identity	<1103> <1125>
	Potency	<111> <1032> <1033> <1034>

Table 1: *USP–NF* resources supporting various analytical assays for release of vaccines

Tools to ensure the quality of medicines that lack public standards

Publicly available analytical tools to verify the quality and authenticity of medicines at any point in the supply chain are essential to protect patients from the threat of SF medicines. Pharmacopeial monographs and supporting reference materials are ideal tools to meet this need by providing test procedures that confirm the identity, purity, and potency of medicines. Any medicine control lab can use these basic tools to help ensure that medicines contain the right active ingredient in the right amount, thereby guarding against two common types of falsification.

The monographs and reference materials also provide a starting package of analytical specifications to help accelerate quality control (QC) setup and regulatory applications for new manufacturers entering the market to fill supply gaps during pandemics[48]. Pharmacopeial monographs and reference materials are available most commonly for generic, off-patent medicines, and typically take 1–2 years to establish due to the need for public consultation processes.

Monographs provide publicly available methods that regulatory authorities and manufacturers can use to assess a medicine's quality objectively. Monographs also can provide analytical tools that help distinguish genuine from falsified products.

Through the WHO's International Meeting of World Pharmacopoeias (IMWP), 10 international pharmacopeias including USP collaborated to publish a dashboard of available international monographs of repurposed drugs under investigation for possible benefit as COVID-19 treatments[49,50]; see **Figure 1**.

In addition to pharmacopeial test procedures designed for laboratory-based testing, analytical tools compatible with field-based screening using portable instruments are also needed. A new screening method for dexamethasone was recently added to GPHF's MiniLab here, and USP has published a resource for evaluating such technologies[51]. Additionally a risk-based tool is available from PQM developed by USP here to help prioritize and identify where to target screening and post market surveillance.

In the early months of the COVID-19 pandemic, many small molecule drugs repurposed as treatments that became the standard of care already had pharmacopeial monographs available. Remdesivir and favipiravir are examples of two antiviral medicines under patent that, as of today, do not have any official monographs. This situation presented the opportunity for a new approach, which is early development

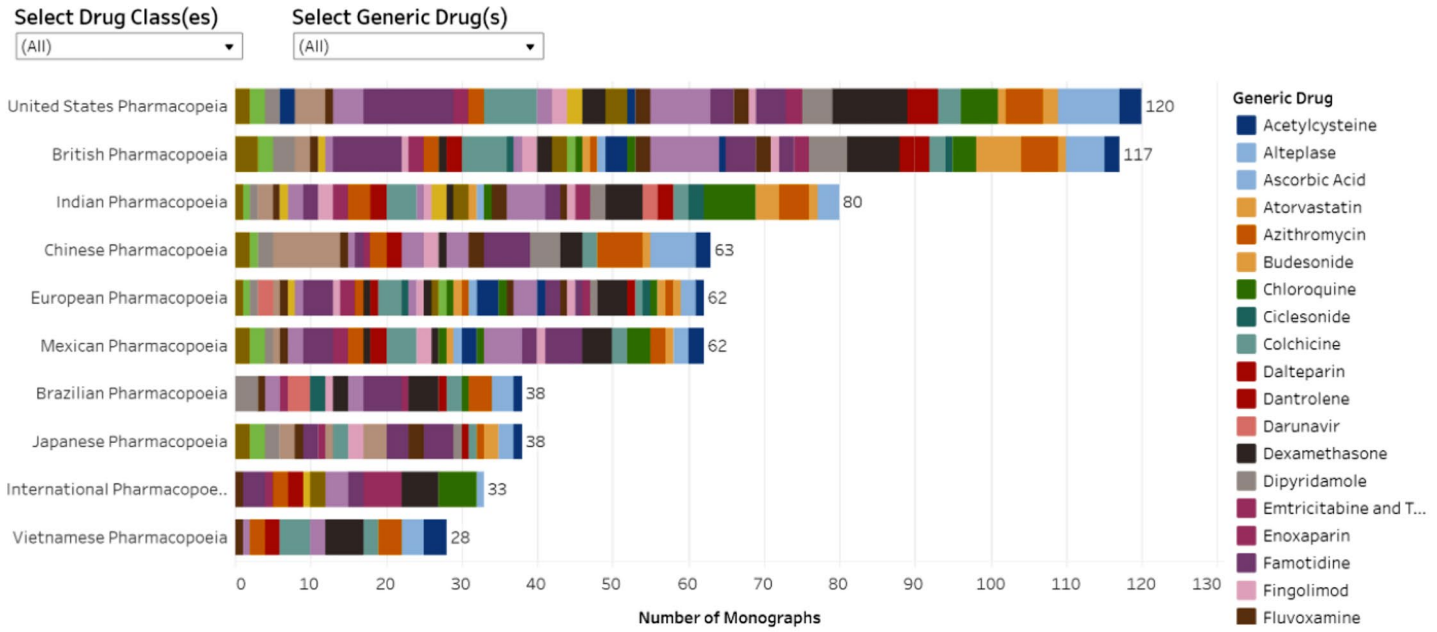


Figure 1: Main dashboard of IMWP, providing information about globally available monographs for treatments under investigation for COVID-19.

of publicly available toolkits featuring validated test methods for identity, purity, and strength to ensure that medicine control labs have basic tools to combat SF medicines. A collection of methods for detecting falsified remdesivir has been developed by USP here complimenting draft monographs being developed by WHO's International Pharmacopeia here as well as the Indian Pharmacopeia Commission.

Mechanisms for accelerated development of complete pharmacopeial monographs with full suites of methods and specifications should be considered for future use in cases of public health emergency. Such mechanisms must be carefully structured to avoid unintentionally putting legitimate manufacturers out of compliance.

As the treatment landscape continues to evolve, there will be additional work and challenges ahead in developing tools to combat SF medicines. With the prospect of more on-patent small molecule drugs being added to the treatment arsenal, the new approaches described above should be considered. Early engagement between innovators and pharmacopeias will be important to ensure that public tools can be available when needed the most. When it comes to monoclonal antibodies, it will be more challenging to develop public tools for these products due to the complexity of analytical characterization and differences across products. Efforts here may be best focused on tools for assessing critical quality attributes that can work across this entire class of therapeutics.

Tools to ensure the quality of infection preventatives

Quality issues with hand sanitizers, such as contamination with methanol, can lead to serious adverse events requiring hospitalization, and may even cause blindness and death. Globally, over 200 quality incidents involving alcohol-based hand sanitizer were reported in 2020[52,53]. In the United States, one batch of contaminated alcohol-based hand sanitizer caused 15 cases of methanol poisoning requiring hospitalization, leading to four deaths and three patients with visual impairments[54].

A different problem is that alcohol-based hand sanitizers can be subpotent if they contain less than the required amount of ethyl or isopropyl alcohol. The FDA's "Do-not-use" list of alcohol-based hand sanitizers includes more than 40 products that are noted for being subpotent[55]. Quality specifications help ensure the correct potency so that the product is not subpotent or super-potent, and also help prevent contamination.

USP is committed to supporting manufacturers, healthcare practitioners, and regulators to protect the quality of alcohol-based hand sanitizer. USP is offering free access to *USP–NF* standards, information, and on-demand education related to producing and compounding quality alcohol-based hand sanitizers[56]. The tools are available here.

Supply chain tools

SF medicines can enter the market for many reasons including an imbalance between supply and demand for the authentic product or its ingredients. Excessive demand and inadequate supply may create opportunities for unscrupulous actors to profit by producing falsified or substandard product. In addition, poor practices along the supply chain or inadequate quality control at manufacturing sites can lead to SF products. These factors are considered supply chain vulnerabilities, and they are exacerbated by the complex global nature of the supply chain with its lack of transparency. USP is working to address these vulnerabilities along two dimensions, as follows.

Increased supply chain transparency

USP has built a data engine called the Medicine Supply Map that acts as an early warning system to identify, characterize, and quantify risk in the upstream pharmaceutical supply chain so that stakeholders can protect patient access to quality medicines. The data model links across more than 10 datasets and millions of datapoints, including data proprietary to USP.

For example, USP's own data show increased interest in dexamethasone-related monographs and reference standards since June 2020, when the news of effectiveness was published[57]. Figure 2 shows average monthly page views for dexamethasone-related monographs along with the number of viewing accounts. Before June 2020, there were 1,333 monthly page views for dexamethasone-related monographs from 225 different accounts. From June 1, 2020, onward, these numbers increased to 2,257 page views from 443 accounts (increases of 70% and 97%, respectively).

In the same time span, average monthly sales of dexamethasone-related reference standards increased by 92% (not shown in figure). This suggests that there was increased interest in dexamethasone among manufacturers during this time period, and manufacturers may have been ramping up analytical R&D and production to meet increased demand.

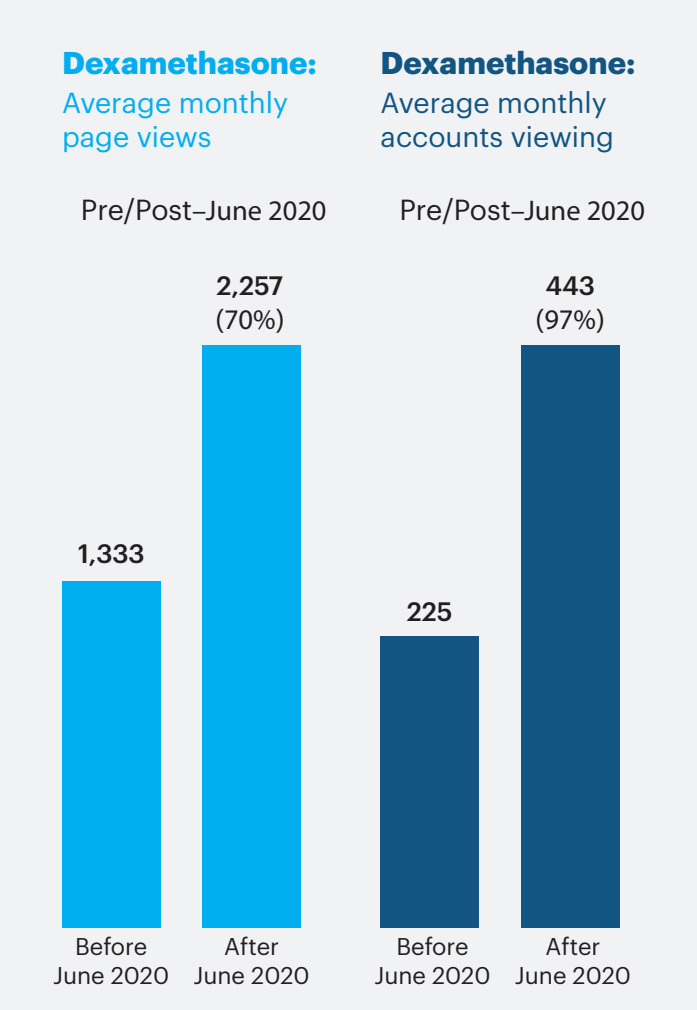


Figure 2: Monthly average page views (left) and accounts viewing (right) for dexamethasone-related monographs before and after news about effectiveness was published in June 2020. Percent increase is shown in parentheses above the right-hand bar in each set.

This process leverages "in-the-field" data gathering through USP's subject matter expert network. The Medicine Supply Map includes more than 1 million medicines globally and leverages a graph-based data model that is capable of tracking quality issues up the supply chain from finished dosage form to API manufacturer. This tool can help stakeholders answer questions such as: How vulnerable is a specific drug product in a specific country from a supply chain standpoint? How might a weather event, new disease outbreak, or political / trade event impact a country's or company's supply chain for the finished drug product and pharmaceutical ingredients? Further information about the USP Medicine Supply Map is available here.

Expanding access to advanced manufacturing technologies

Advanced manufacturing technologies, such as pharmaceutical continuous manufacturing (PCM), offer one solution to address the dual problems of "long" supply chains transcending multiple geographies (hence making them difficult to oversee) and the need for more rigorous quality controls along each step. USP has led thinking in advancing the science of PCM, holding a roundtable in 2016 that led to the creation of an Expert Panel and the publication of a Stimuli article. USP has now engaged in scientific collaborations with Rutgers University's Engineering Research Center for Structured Organic Particulate Systems, CONTINUUS Pharmaceuticals, and others to advance science and capability building in this space. Further information about USP activities on PCM is available here.

Conclusion

As with previous pandemics, COVID-19 has increased the vulnerability of global supply chains to entry of SFHP including medicines, vaccines, and infection preventatives. Standards and toolkits are needed to help protect these products—and ultimately to help protect people worldwide—from this threat during and after the COVID-19 pandemic. USP is providing a number of these toolkits as outlined in the text above, either in cooperation with other organizations (for example, the IMWP dashboard) or as a single institution.

Acknowledgements

The authors wish to thank the following individuals for their assistance with this paper: Loredana Jinga for providing information on the hand sanitizer toolkit, Jennifer Strohm for her review of the draft, and Shreyash Suryawanshi for the access data on the dexamethasone-related monographs.

References

1. WHO. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva, Switzerland: World Health Organization, 2017.
2. WHO. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva, Switzerland: World Health Organization, 2017.
3. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. Br J Clin Pharmacol. 2014;78(2):218-243.
4. Rojas-Cortés R. Substandard, falsified and unregistered medicines in Latin America, 2017-2018. Rev Panam Salud Publica. 2020;44:e125.
5. WHO. Substandard and falsified medical products. Geneva, Switzerland: World Health Organization, 2018. c.
6. WHO. Seventieth World Health Assembly update, 29 May 2017. Geneva, Switzerland: World Health Organization. https://www.who.int/news/item/29-05-2017-seventieth-world-health-assembly-update-29-may-2017.
7. Ozawa S, Evans DR, Bessias S, et al. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: A systematic review and meta-analysis. JAMA Netw Open. 2018;1(4):e181662.
8. Pisani E, Nistor AL, Hasnida A, Parmaksiz K, Xu J, Kok MO. Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania. Wellcome Open Res. 2019 Apr 16;4:70.
9. Newton PN, Bond KC, on behalf of 53 signatories from 20 countries. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. Lancet Glob Health. 2020 Jun 1;8(6):e754-e755. https://doi.org/10.1016/S2214-109X(20)30136-4. Epub 2020 Apr 9. Erratum in: Lancet Glob Health. 2020 Jul;8(7):e900. PMID: 32278364; PMCID: PMC7158941.
10. PAHO. Post-authorization surveillance of medical products during a pandemic emergency, 21 July, 2020. Washington, D.C.: Pan American Health Organization. https://iris.paho.org/bitstream/handle/10665.2/52578/PAHOHSSMTCOVID-19200026_eng.pdf?sequence=1&isAllowed=y.
11. CIDRAP. US agents seize shipments of fake Tamiflu. Center for Infectious Disease Research and Policy, December 20, 2005. https://www.cidrap.umn.edu/news-perspective/2005/12/us-agents-seize-shipments-fake-tamiflu.
12. Green MD, Nettey H, Wirtz RA. Determination of oseltamivir quality by colorimetric and liquid chromatographic methods. Emerg Infect Dis. 2008;14(4):552-556.
13. Cockburn R. Death by dilution. The American Prospect. November 20, 2005. https://prospect.org/features/death-dilution/
14. Jia H, Carey K. Chinese vaccine developers gain WHO imprimatur. Nature Biotechnol. 2011;29(6):471-472.
15. Vaccine scandal and confidence crisis in China (editorial). Lancet 2018;392(10145):P360. https://doi.org/10.1016/S0140-6736(18)31695-7
16. Salmon DA, Dudley MZ, Glanz JM, Omer SB. Vaccine hesitancy: Causes, consequences, and a call to action. Am J Preventive Med. 2015;49(6):S391-S398. https://www.sciencedirect.com/science/article/abs/pii/S0749379715003141
17. WHO. Ten threats to global health in 2019. World Health Organization, 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019
18. IDDO. Medical Product Quality Report – COVID-19 vaccine issues. 18 March 2021. Infectious Diseases Data Observatory. https://www.iddo.org/sites/default/files/publication/2021-03/Medical%20Product%20Quality%20Report_COVID-19%20VACCINE%20issues_March2021_V3.pdf
19. FDA. Fraudulent Coronavirus Disease 2019 (COVID-19) Products. U.S. Food & Drug Administration. https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products
20. FDA. FDA alerts health care professionals and compounders of potential risks associated with the compounding of remdesivir drug products. U.S. Food & Drug Administration, February 4, 2021. https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-and-compounders-potential-risks-associated-compounding#:~:text=FDA%20urges%20compounders%20not%20to,or%20quality%20of%20compounded%20drugs
21. FDA. FDA News Release. U.S. Food & Drug Administration, January 26, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-place-all-alcohol-based-hand-sanitizers-mexico-import
22. Kelley A. Widespread fake N95 mask scam under investigation. The Hill, February 10, 2021. https://thehill.com/changing-america/well-being/medical-advances/538360-widespread-fake-n95-mask-scam-under
23. FDA. Protecting Americans from COVID-19 scams (written testimony only). U.S. Food & Drug Administration, July 21, 2020. https://www.fda.gov/news-events/congressional-testimony/protecting-americans-covid-19-scams-written-testimony-only-07212020
24. Wright L. Officials warn of fake COVID-19 vaccines. DW (Deutsche Welle), January 4, 2021. https://www.dw.com/en/officials-warn-of-fake-covid-19-vaccines/a-56123830
25. EUROPOL. Early warning notification – Vaccine-related crime during the COVID-19 pandemic. EUROPOL, December 4, 2020. https://www.europol.europa.eu/early-warning-notification-vaccine-related-crime-during-covid-19-pandemic-0
26. EUROPOL. Medicines and doping substances worth € 73 million seized in Europe-wide operation. EUROPOL, December 10, 2020. https://www.europol.europa.eu/newsroom/news/medicines-and-doping-substances-worth-%E2%82%AC73-million-seized-in-europe-wide-operation
27. CDSCO. Drug alerts. Central Drugs Standard Control Organization, Government of India. https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
28. Rana Y. Punjab: Doctors refuse to wear 'substandard' PPE kits in Amritsar, minister orders probe. Times of India, April 26, 2020. https://timesofindia.indiatimes.com/city/amritsar/punjab-doctors-refuse-to-wear-substandard-ppe-kits-in-amritsar-minister-orders-probe/articleshow/75385827.cms
29. Remdesivir batch withdrawn due to inferior quality: Maharashtra government. Economic Times, September 23, 2020. https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/remdesivir-batch-withdrawn-due-to-inferior-quality-maharashtra-government/articleshow/78274741.cms?from=mdr
30. Chemists facing problem of plenty as demand for antiviral

drugs falls. The Hindu, January 6, 2021. https://www.thehindu.com/news/national/karnataka/chemists-facing-problem-of-plenty-as-demand-for-antiviral-drugs-falls/article33504951.ece

31. Chemists urge pharma firms to take back huge stocks of Covid medicines. The Hans India, January 5, 2021. https://www.thehansindia.com/bengaluru/chemists-urge-pharma-firms-to-take-back-huge-stocks-of-covid-medicines-665370
32. India's CDSCO flags 25 drugs as not of standard quality. The pharma letter, December 6, 2020. https://www.thepharmaletter.com/article/india-s-cdsco-flags-25-drugs-as-not-of-standard-quality
33. Fake pharmaceutical industry thrives in West Africa. BBC, July 14, 2020. https://www.bbc.com/news/world-africa-53387216
34. IDDO. Medical product quality report – COVID-19 issues. Issue 1, January to June 2020. Infectious Diseases Data Observatory. https://www.iddo.org/sites/default/files/publication/2020-08/Medical%20Product%20Quality%20Report_Covid-19%20Issues_Issue%201%20Jan-June%202020_Main%20text%20plus%20annexes_12aug2020.pdf
35. Mosoro E, Wilson AN, Homer CSE, Vogel JP. Assessing the quality of antenatal corticosteroids in low- and middle-income countries: A systematic review. PLoS One 2020;15(12):e0243034. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7714108/pdf/pone.0243034.pdf
36. Fake medicine giving ASEAN a headache. The Asean Post, September 7, 2019. https://theaseanpost.com/article/fake-medicine-giving-asean-headache
37. Joint Statement, 14th ASEAN Health Ministers Meeting, 29 August 2019, Siem Reap, The Kingdom of Cambodia. https://asean.org/storage/2019/09/14th-AHMM_Joint-Statement_FINAL1.pdf
38. United Nations. Transnational Organized Crime in Southeast Asia: Evolution, Growth and Impact. United Nations Office on Drugs and Crime (UNODC), 2019. https://www.unodc.org/documents/southeastasiaandpacific/Publications/2019/SEA_TOCTA_2019_web.pdf
39. BBC News [Internet]. Tratamiento del coronavirus | El alarmante negocio de medicamentos falsos que crece por la pandemia de covid-19. https://www.bbc.com/mundo/noticias-52238655. BBC, April 27, 2020.
40. Ministerio de Salud (Minsa) de Perú [Internet]. Minsa: Cuatro toneladas de medicamentos falsificados fueron incautadas durante la emergencia por COVID-19. February 11, 2021. http://www.digemid.minsa.gob.pe/Main.asp?Seccion=3&IdItem=2251.
41. Gobierno de Mexico [Internet]. La Cofepris alerta sobre la falsificación del medicamento plaquenil® (hidroxicloroquina). June 26, 2020. https://www.gob.mx/cofepris/articulos/la-cofepris-alerta-sobre-la-falsificacion-del-medicamento-plaquenil-hidroxicloroquina?idiom=es.
42. Gobierno de Mexico [Internet]. La Cofepris alerta sobre la comercialización ilegal de productos falsificados de ivermectina e ivermin. November 20, 2020. https://www.gob.mx/cofepris/es/articulos/la-cofepris-alerta-sobre-la-comercializacion-ilegal-de-productos-falsificados-de-ivermectina-e-ivermin?idiom=es.
43. Ministério da Saúde (BR), Agência Nacional de Vigilância Sanitária [Internet]. Anvisa alerta para a falsificação de medicamentos. Brasília, DF: Anvisa; 2020. September 6, 2020. https://www.gov.br/pt-br/noticias/saude-e-vigilancia-sanitaria/2020/06/anvisa-alerta-para-a-falsificacao-de-medicamentos.
44. Ministério da Saúde (BR), Agência Nacional de Vigilância Sanitária [Internet]. Fiscalização - Consulta a Produtos Irregulares Covid-19. Brasília, DF: Anvisa; September 21, 2020. https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus/fiscalizacao/fiscalizacao.
45. WHO. Draft landscape and tracker of COVID-19 candidate vaccines. World Health Organization, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
46. USP. Accelerating the rollout of COVID-19 vaccines: A how-to guide for national regulatory authorities in low- and middle-income countries. U.S. Pharmacopeia. https://www.usp.org/sites/default/files/usp/document/our-work/global-public-health/covid-19-vaccines-for-lmics.pdf
47. USP. COVID-19 vaccine handling toolkit: Operational considerations for healthcare practitioners. U.S. Pharmacopeia, March 2021. https://www.usp.org/covid-19/vaccine-handling-toolkit
48. Murimi-Worstell IB, Ballreich JM, Seamans MJ, Alexander GC. Association between US Pharmacopeia (USP) monograph standards, generic entry and prescription drug costs. PLoS ONE. 2019;14(11):e0225109.
49. USP. Interactive dashboard of COVID-19 drugs in world pharmacopeias. U.S. Pharmacopeia, 2021. https://www.usp.org/covid-19/treatment-and-prevention/world-pharmacopeias-dashboard
50. WHO. Health product and policy standards. World Health Organization. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia/IMWP
51. USP. General Chapter <1850> Evaluation of Screening Technologies for Assessing Medicine Quality. U.S. Pharmacopeia - National Formulary (USP-NF), November 1, 2020.
52. IDDO. Medicine Quality Monitoring Globe. Infectious Diseases Data Observatory, 2020. https://www.iddo.org/medicine-quality-monitoring-globe
53. CDSCO. Alerts: Drug alert list for month of December 2020 (11 Jan 2021). Central Drugs Standard Control Organization. https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
54. CDC. Serious adverse health events, including death, associated with ingesting alcohol-based hand sanitizers containing methanol. Centers for Disease Control and Prevention, August 14, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm
55. FDA. FDA updates on hand sanitizers consumers should not use. U.S. Food & Drug Administration, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use
56. USP. Supporting quality hand sanitizer production. U.S. Pharmacopeia, 2021. https://go.usp.org/quality_hand_sanitizer
57. WHO. Coronavirus disease (COVID-19): Dexamethasone. World Health Organization, June 25, 2020. https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-dexamethasone