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OPINION

After counterfeit Avastin®—what have we learned and what can be done?

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Abstract | Three years have passed since the FDA announced that it had detected counterfeit versions of the injectable anticancer drug bevacizumab (Avastin®, Genentech, USA) in the US drug-supply chain. Following this discovery, almost 1,000 FDA warning letters were sent to physicians and medical practices in 48 different states and two US territories, as more batches of counterfeit Avastin were uncovered. In response, criminal prosecutions have been pursued against certain distributors and clinicians, and other individuals who trafficked, sold, purchased, and/or administered an unsafe and ineffective treatment while also defrauding the government. Although limited and targeted legal action has been taken, patients potentially affected by this seminal patient safety event have not been appropriately identified. Hence, despite the clear and documented patient-safety and public-health risks posed by the transnational criminal trade in counterfeit medicines, the case study of counterfeit bevacizumab detection in the USA demonstrates the continued lack of information, knowledge, and solutions that would be necessary to protect those who are most affected—the patients. In response, we call for greater investment in multisector, multistakeholder strategies to enhance surveillance for counterfeit medicines and enable improvements in communication of risk information, to better protect patients with cancer.

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Introduction

On 14 February 2012, the FDA notified health-care professionals and patients via its website that it had detected counterfeit versions of the biological anticancer drug bevacizumab (Avastin®, Genentech, USA) in the USA.[1] Bevacizumab, a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), is an expensive, injectable angiogenesis inhibitor that is used in combination with chemotherapy to inhibit or delay tumour growth. Bevacizumab is used to treat a variety of cancers, is administered in clinics, hospitals, and medical practices, and generated around US$6 billion in sales in 2013, making it the ninth highest-grossing drug worldwide.[2] The counterfeit versions of bevacizumab identified by FDA had no active pharmaceutical ingredient (API), and instead contained substances ranging from corn starch and salt to common solvents, such as acetone.[1,3–5] The term 'counterfeit' is often used interchangeably with the terms 'falsified' or 'fraudulent' to refer to medicines that are substandard, ineffective, or adulterated, and made with criminal intent to deceive regarding the authenticity or origin of the medicine. Investigations revealed that batches of counterfeit bevacizumab, which were confirmed as unsafe and ineffective, had traversed a complex network of wholesalers and countries, including Turkey, Switzerland, Denmark, the UK, and Canada, before finally arriving in US clinics.[3,6] Although only one version of bevacizumab is FDA-approved, fake and unauthorized versions were nevertheless purchased by US medical clinics from foreign suppliers through the 'grey market' (defined as a secondary wholesale market outside of the traditional primary sourcing chain), in violation of the US Food, Drug and Cosmetic Act.[1,7]

Competing interests
T.K.M. and B.A.L. are reimbursed for travel to one Partnership for Safe Medicines annual conference each year. T.K.M. is also a non-compensated member of the academic advisory panel of the Alliance for Safe Online Pharmacies. R.C. and C.G. declare no competing interests.

Initial FDA warnings turned out to be just the beginning of a much larger and more complex failure in the international and domestic drug-safety system. Notably, 3 years after the first detection of counterfeit bevacizumab in the USA, the public health and patient safety repercussions remain poorly understood. To better understand this important event in the history of US drug safety, we conducted a multidisciplinary assessment of the counterfeit bevacizumab incident using available regulatory and legal data in the hopes of informing future efforts to prevent counterfeit cancer medication from adversely affecting patients.

Regulatory response

On 10 February 2012, the FDA sent warning letters to 19 medical practices that it suspected had purchased counterfeit Avastin®.[1] The FDA was originally notified of a potential supply chain breach by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) in December 2011, after the MHRA investigated a report from the Danish Medicines Agency regarding counterfeit Avastin® being sold from a Danish distributor (CareMed) to a British wholesaler (River East Supplies).[8,9]

The FDA letters identified several suspect distributors (Clinical Care, Quality Speciality Products, Montana Health Care Solutions, Bridgewater Medical, Volunteer Distribution, River East Supplies, Richard's Pharma [trading as Richard's Services], Warwick Healthcare Solutions, Ban Dune Marketing), none of which were authorized to distribute Avastin®.[1] Specifically, these warning letters informed medical practices that they had purchased products sold or distributed by one of the above distributors, and that "most, if not all" of these products (including counterfeit versions of bevacizumab) had not been approved by the FDA and/or were probably counterfeit versions, placing patients' health at risk.[10] The FDA also reported batch numbers of suspected counterfeit Avastin®, requested practices to cease using and retain all products purchased, and provided information for reporting suspected criminal activity and adverse events.[1] However, only a few months later, in April 2012, an

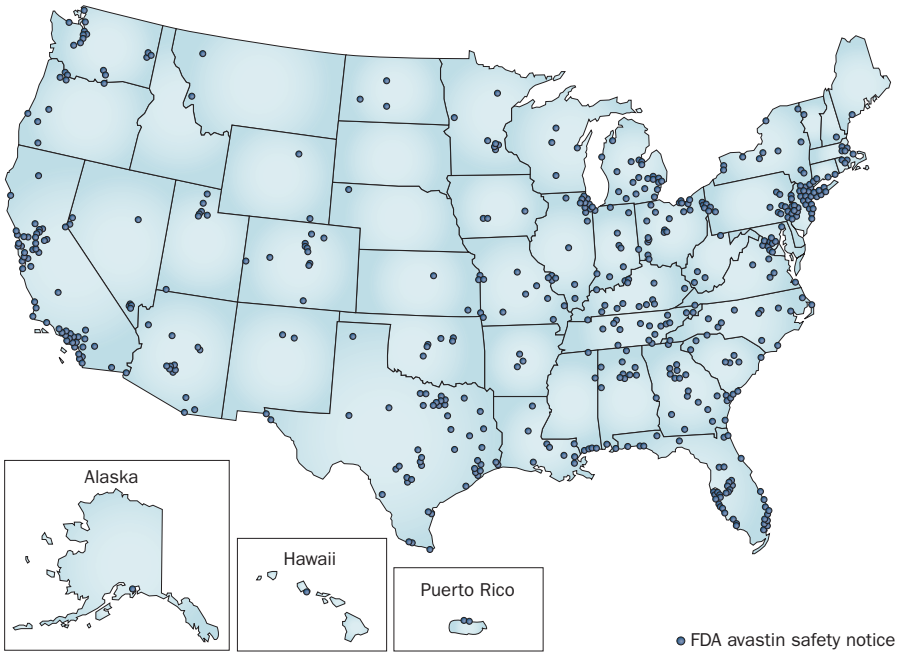

Figure 1 | Visual depiction of a total of 949 FDA safety notifications that were sent to 932 physicians and/or clinics in 795 zip codes from 2012 to 2013. These are depicted at the individual zip-code level.

additional 68 warning letters were sent, followed by 57 in June 2012, and another 23 in September 2012. In total, based on our analysis of publicly available data from the FDA, in 2012, warnings were sent to 168 physicians and/or clinics (151 distinct practices) across 33 states.[10] A number of implicated wholesale distributors who were listed in these warnings were also identified as being owned by or affiliated with a popular Canadian online pharmacy, CanadaDrugs.com, another grey market source of prescription medications.[11]

Despite the earlier warnings, on 5 February 2013 the FDA announced that it had detected another batch of counterfeit and unapproved Avastin®, this time distributed by a different US-based supplier, Medical Device King (also known as Pharmalogical Inc.) and packaged as a Turkish version under the trade name Altuzan™.[10,12] The FDA confirmed that these products contained no API, and a new round of warnings followed: 781 medical practices were notified across 46 states as well as the US territories of Puerto Rico (three notices) and the Virgin Islands (one notice).[10]

The FDA again informed medical practices to immediately cease using these products and to surrender them to the FDA Office of Criminal Investigations (OCI), provided suspected counterfeit batch numbers, and issued a public-service announcement providing health-care professionals with guidance on how to ensure the safety of their patients. The guidance included warnings not to trust deeply discounted offers on drugs, to carefully inspect products and packaging for counterfeit risk features, and to monitor for patient complaints and adverse events.[10]

In total, our analysis found that 949 FDA safety notifications were sent to 932 physicians and/or clinics across 795 zip codes in 2012 and 2013. Warning notices had a broad US geographical distribution (Figure 1), were sent to 48 states and two territories, and were highly concentrated in California (17.7% of all notices), Texas (9.2%), Florida (8.5%), and New York (8.2%). The warning letters identify clinical locations where counterfeit Avastin® was possibly purchased and administered, and provide some indication of the potential scope of counterfeit Avastin® distribution, as well as the accompanying safety risk. However, data on the exact number of patients who received counterfeit Avastin® are not available for further analysis.

Legal response—prosecutions

The detection of counterfeit Avastin® has had legal consequences for certain wholesaler and provider participants involved in this patient-safety breach. Assessing published criminal and civil cases associated with the counterfeit bevacizumab incident using legal databases PACER (Public Access to Court Electronic Records) and Westlaw, we identified 11 closed or ongoing prosecutions, after reviewing criminal complaints or indictments, plea agreements, sentencing documents, and civil settlements (Table 1). All cases were filed by federal prosecutors, mostly in cooperation with OCI, and many involved associated defendants (for example, a supplier indicted in one case and the purchasing physician or medical practice indicted in another). Defendants comprised a mix of domestic and international suppliers, physicians, a pharmacist, and clinic staff. Unsurprisingly, many defendants are those specifically named in, or recipients of, FDA warning letters, including distributors (Montana Healthcare Solutions, Ban Dune Marketing, Richard's Pharma, and Medical Device King), and purchasing clinics and physicians (East Tennessee Cancer & Blood Center, McLeod Cancer and Blood Center, Alvarado Medical Plaza Compounding Pharmacy). Prosecutions have occurred in California, Maryland, Montana, Missouri, New Mexico, Tennessee, and New York federal courts against defendants located in multiple states. Criminal prosecutions include charges for distribution of misbranded or adulterated prescription drugs, receiving and/or introducing a misbranded drug with intent to defraud or mislead, federal fraud and abuse claims for violating the False Claims Act, trafficking and smuggling of counterfeit merchandise into the USA, and mail and wire fraud. Although serious charges, none of the above legal claims directly relate to personal injury associated with patient-safety adverse events.

Collectively, analysis of these cases reveal some concerning details. For example, certain defendants were actively acting as sellers and purchasers of counterfeit medicines for several years before the counterfeit bevacizumab was detected. Sellers often shipped to multiple states, were aware that their products were not being properly stored or shipped (for instance, not maintaining cold storage), and some even had direct knowledge of patient adverse events.[13,14] Furthermore, defendants such as Dr William Kincaid and Patricia Sen knowingly continued to purchase and conceal counterfeit products even after their practice nurses alerted them to safety concerns.[15–17] Additionally, all but one of the named physicians who were defendants in prosecutions were recipients of FDA warning letters, and documents reveal

Table 1 | Court cases resulting from the counterfeit bevacizumab incident*

Case	Defendants and company (position therein)	Location of US District Court	Cost of counterfeit drugs purchased	Punishment
USA versus Anindya Kumar Sen *et al.* (2:13-CR-56)	Dr Anindya Kumar Sen (owner, Managing Physician) and spouse, Patricia Posey Sen (Office Manager), East Tennessee Cancer & Blood Center	Eastern District of Tennessee at Greeneville	US$3 million	Anindya Sen: 3 years of probation; $100,000 fine; must submit medical practice for inspection Patricia Sen: 4 years of probation; $200,000 fine; can't work for any medical practice without permission of probation officer
USA versus Scully *et al.* (2:2014-CR-00208)	William Scully (President) and Shahrad Rodi Lameh (Vice President), Pharmalogical Inc. company (trades as Medical Device King)	Eastern District of New York	NA	Criminal case continued until 15 May 2015
USA versus Paul Daniel Bottomley (CR-13-04-BU-DLC)	Paul Daniel Bottomley (owner), Montana Health Care Solutions	Montana, Butte Division	NA	6 months of house arrest; 5 years of probation; $4,454,278.17 total forfeitures (comprised of $1.08 million in cash, 10 parcels of land in Gallatin County, and 2011 Aston Martin V-12); $100 special assessment for felony offense under 18 USC 3013; 200 hours of community service; $1,088,378.17 civil forfeiture to USA
USA versus James Newcomb *et al.* (4:12CR00009RWS-1)	James Newcomb (owner, President) and Sandra Behe (employee), Ban Dune Marketing Dr Abid Nisar (physician), private practice	Eastern District of Missouri, Eastern Division	NA $352,504 (Dr Nisar)	Newcomb: 24 months in prison; $1.4 million in criminal and civil penalties; forfeiture of Land Rover Behe: 5 years of probation; 200 hours of community service Nisar: 2 years of probation; 200 hours of community service; $25,000 criminal fine; $1,000,336 repayment to government health programmes for false claims; medical licence suspended in Illinois, and in Missouri for 5 years; banned from participation in federal health-care programmes for 7 years
USA versus Isabella Martire (8:11-CR-00373-DKC-1)‡	Dr Isabella Martire (physician), private practice	Maryland, Greenbelt	$200,000	Pending
USA versus Mohamed Basel Aswad (2:14-CR-03274-RB)	Physician (private practice)	District of New Mexico	NA	3 years probation; $1,298,543.00 restitution to Medicare & Tricare; $750,000 forfeiture to US government
USA versus Ozkan Semizoglu & Sabahaddin Akman (4:14-CR003-AGF/TCM)	Ozkan Semizoglu (owner, Foreign Trade Director) and Sabahaddin Akman (majority owner), Ozay Pharmaceuticals	District of Missouri, Eastern Division	Exported $1.2 million worth of medication to the US	Both plead guilty: Ozkan 27 months imprisonment and $200 criminal fine; Akman to be sentenced 23 January 2015; Akman: 30 months imprisonment; $150,000 fine for smuggling misbranded and adulterated cancer treatments into US; $150,000 forfeiture before sentencing
USA versus William Ralph Kincaid (2:12-CR-116-JRG-DHI)	Dr William Ralph Kincaid (President, majority owner, and physician), McLeod Cancer and Blood Centre Drs Milard Lamb and Olubenga Famoyin (physicians), private practice	District of Tennessee at Greenville	>$2 million (Kincaid) NA	Kincaid: 24 months imprisonment; $10,000 criminal fine; $100 special assessment; $2.55 million civil settlement; 10-year exclusion from federal health-care programmes; Lamb and Famoyin: not charged criminally, but each paid an $850,000 civil settlement
USA versus Michael Combs (2:12-CR-94)	Michael Dean Combs (employee), McLeod Cancer and Blood Center	District of Tennessee, Greenville	$2.5 million	3 years of probation; 250 hours of community service; $4,000 fine
USA versus Richard J. Taylor (4:13-CR-00297-RWS)	Richard Taylor (owner, supplier), Richard's Pharma	District of Missouri, St Louis	NA	18 months of imprisonment; $800,000 fine; $3.2 million in forfeitures
USA versus Alvarado Medical Plaza Pharmacy *et al.* (3:13-CR-04-295)	Alvarado Medical Plaza Pharmacy, Inc. William Burdine (pharmacist-owner), Alvarado Medical Plaza, Inc.	Southern District of California, San Diego	$750,000	Burdine: liable for restitution in amount of $1,004,282.04 (jointly and severally with pharmacy); 5 years probation, $100 assessment, and jointly and severally liable for restitution in amount of $1,004,282.04

*Updated as of 14 January 2015. ‡Case occurred before FDA notifications in 2012, but defendant identified as sourcing counterfeit bevacizumab, and was a recipient of an FDA warning notice in 2012. Abbreviation: NA, not applicable.

that the primary motivation for purchasing counterfeit versions was to secure lower pricing in order to generate profits. Indeed, prosecuted clinic employees or clinicians were often complicit with illegal distributors who facilitated access to a complex international network for sourcing counterfeit bevacizumab, by deliberately falsifying documents and concealing shipments.[18,19]

Legal documents also disclose that other counterfeit and unapproved drugs were being sold by these unauthorized distributors and purchased by practices, including other cancer treatments (rituximab, oxaliplatin, zoledronic acid, gemcitabine, and pegfilgrastim), as well as prescription drugs and devices, which were illegally offered and sold throughout the USA.[13,20,21] The effects of these other counterfeit products on patient safety has not been widely reported, and, unlike counterfeit bevacizumab, has not been the subject of specific FDA warning letters.

Unanswered questions

We began our investigation with some crucial questions regarding the penetration of counterfeit bevacizumab into the US drug-supply chain, but our review left us with more questions than answers. First, we wanted to explore what data were available from this seminal drug-safety event, and whether lessons could be learned to improve the safety of patients with cancer. Specifically, we wished to examine whether the available data were robust enough to provide a more-complete picture of the underlying causes and scope of the breach in the drug-supply chain, which patient populations were adversely affected, and whether such data could inform public-health interventions, regulatory action, and policy responses needed to prevent counterfeit cancer medications from harming patients in the future. However, our assessment left us with a disconcerting conclusion—the medical, public-health, and patient communities continue to lack the information and tools needed to appropriately assess the counterfeit bevacizumab incident, and similarly lack adequate protection should counterfeit drugs penetrate the US drug-supply chain again.

We base this conclusion on three main findings. First, a lack of peer-reviewed literature exists on the topic—the vast majority of information we reviewed for this study was from 'grey' literature (such as investigative journalism), the FDA website, and legal documents, rather than empirical study. Second, validated data needed to accurately assess the actual effect of this event are generally lacking—FDA warnings and legal prosecutions provide the only readily available data on counterfeit bevacizumab detection, and have their own limitations. Finally, relatively few prosecutions have occurred despite the nationwide distribution of FDA warnings. Although nearly 1,000 FDA safety notices were issued, only 18 individuals have been prosecuted, with a maximum prison sentence of 2 years, and with some defendants sentenced no more than probation or house arrest following conviction (Table 1). Collectively, these limitations mean that the events associated with counterfeit bevacizumab supply are only partially understood.

Some 3 years after the first warning notices were issued by the FDA, we are no closer to ascertaining basic, but crucial, information, such as how much counterfeit bevacizumab actually entered the US market, or the number of patients exposed and adversely affected. Indeed, our review found only three governmental civil settlements for restitution, meaning that patients have not actively sought recourse for possible harm. This finding probably indicates that the patients who were administered counterfeit bevacizumab were completely unaware of possible exposure or potential risks, and might have suffered adverse consequences that went undetected and unreported—a common circumstance in cases involving counterfeit drugs.[22,23]

Our analysis of existing data had certain limitations. For example, court records related to counterfeit bevacizumab prosecutions might not have been available for public scrutiny owing to the ongoing nature of investigations or as a result of confidential settlement agreements. Furthermore, FDA warning letters serve as a poor proxy for assessing the full effects of, and exposure to, counterfeit bevacizumab in US patients, but are the only data sources available providing geographically specific information, to our knowledge. This lack of critical information for patients, clinicians, regulators, and law-enforcement agencies to act on points to one clear conclusion—we still do not have optimal approaches to obtaining necessary information on counterfeit-drug incidents and their effects on patient safety.

Challenge of the grey market

The detection of counterfeit bevacizumab was a watershed moment in the history of US drug safety, and has exposed vulnerabilities of the globalized drug-supply chain to counterfeit-drug penetration. However, counterfeit medicine detection in the USA is not a new phenomenon, with other examples including the detection and confiscation of 13,000 up-labelled counterfeit versions of erythropoietin, resulting in multiple criminal indictments.[24] Patient-safety events associated with counterfeit versions of bevacizumab have also been reported outside of the USA, including acute postoperative endophthalmitis following off-label use of what was thought to be bevacizumab to treat macular degeneration in China, and the detection of a fungal growth inside a bottle of counterfeit bevacizumab in India.[25–27] These incidents demonstrate the existence of a complex global public-health problem—the transnational criminal trade in counterfeit medicines.[7,28]

Incidents associated with counterfeit bevacizumab in the USA constitute a relatively small proportion of the estimated multi-billion dollar transnational criminal enterprise in trafficking of counterfeit medicines,[4,5,29,30] as highlighted in a report published by the Institute of Medicine in 2013.[23] As an example, the presence of fake, substandard and counterfeit versions of life-saving anti-infective drugs (including high detection rates of counterfeit antimalarial drugs in sub-Saharan Africa and Southeast Asia) is a long-standing concern in global public health, with large-scale effects on populations.[31–33] Despite recognition of the problem as early as 1988 by the WHO, the international community has failed to join together to adopt solutions needed to address this serious globalized pharmaceutical crime.[4,5,23,34]

Detection of counterfeit bevacizumab in US medical clinics, despite the presence of one of the most highly regulated drug-supply systems in the world, raises serious concerns about the broader integrity and security of the global drug-supply chain, as well as the vulnerabilities of domestic pharmaceutical markets.[28] Specifically, the transnational importation path of counterfeit bevacizumab exposed the risks of sourcing through the pharmaceutical grey market—a secondary, quasi-regulated channel of distribution, characterized by drug manufacturers as unofficial, unauthorized, or unintended, where the practices of aggressive marketing and price gouging (pricing above the market price when no alternative retailer is available) of drugs subject to supply shortages have previously raised serious concerns.[35] The grey market creates a conduit for diverted or stolen drugs, enables the adulteration of cancer medicines, and acts as an entry point for counterfeit drugs into controlled drug markets.[6,7,24,36] Despite these risks, the counterfeit bevacizumab incident has not led to meaningful reform or robust regulation of this vulnerable sector that is often relied upon for drug sourcing and procurement.

The reported involvement of Canadadrugs.com, an online pharmacy that has been associated with the supply of counterfeit or unapproved drugs, and that recently had its wholesale licence suspended by Health Canada, indicates that nontraditional channels of the grey market can also enable the international trade in counterfeit medicines.[11] Studies have shown that illegal, 'no prescription' online pharmacies form an unauthorized distribution channel for counterfeit medicines, employing the tactics of aggressive and/or misleading marketing and highly discounted drug pricing to sell a wide variety of medical products directly to patients.[6,37–41] Despite

documented incidents of patient injury and/or death resulting from online drug purchasing and the apparent involvement of Canadadrugs.com in counterfeit bevacizumab sourcing, regulation of illicit online pharmacies by aggressive prosecution or policy reform has not occurred.[11,22,42,43]

Some efforts have been made to identify limitations of the current drug-safety system in the wake of the counterfeit bevacizumab incident, but with questionable results. In 2013, a joint expert working group was convened to consider reducing the threat of counterfeit or unapproved drugs in clinical settings. The working group was co-hosted by the Brookings Institute and the FDA, and attended by physicians, other healthcare professionals (nurses, physician assistants), medical licensing boards, drug manufacturers, patient advocacy organizations, healthcare provider and insurance companies, malpractice, insurers and counterfeit drug researchers.[44] Although several issues were discussed, including improving education on the issue, engaging health-care providers in surveillance and/or health promotion, increasing publicity and information exchange on the risks of counterfeit drugs, and creating disincentives for purchasing counterfeit drugs, the outcome of this working group is unclear.[44] Consensus on key topics was not reached, except in the acknowledgement that clinicians and the public continue to remain unaware and to lack knowledge of the relevant issues and risks, even after the counterfeit bevacizumab incident.

Policy responses

The detection of counterfeit Avastin® in the USA highlights key concerns that need to be addressed through greater commitment to drug surveillance, and through efforts to improve the affordability of, and access to, oncology drugs. From a surveillance perspective, detection of counterfeit bevacizumab was aided by obvious defects in packaging and labelling, with incorrect logos misidentifying the manufacturer as Roche rather than Genentech, erroneous batch numbers, and inappropriate foreign language markings.[1] For example, products claiming to be the unapproved Turkish 'Altuzan™' version of Avastin® were clearly not approved for use in the USA.[12] Had counterfeiters not constructed their products so poorly, identification and interdiction could have been substantially more difficult, leading to more-serious patient-safety consequences. Although counterfeit versions of bevacizumab were easily identifiable, clinics nevertheless failed to adequately report identification to the FDA, which might have enabled a quicker, proactive response.

Surveillance might have been complicated by the clinical use of bevacizumab in combination with first-line or second-line chemotherapy agents, and its relative tolerability and manageable safety profile for certain cancers (although it carries a 'black-box warning'—the strongest FDA-mandated drug-packaging written warning—for gastrointestinal perforation, wound-healing complications, and haemorrhage). The use of bevacizumab in combination therapies makes it difficult to detect specific adverse events, or the administration of an inactive agent.[45–48] Indeed, although thousands of warnings were issued by the FDA, only a few, isolated incidents of adverse events were reported publicly similar to the case of detections of counterfeit erythropoietin in 2002.[24,49] Hence, current drug-safety surveillance measures seem to be inadequate for counterfeit-drug risk assessment, detection and prevention. The Drug Supply Chain Security Act (Title II, Drug Quality and Security Act, 2013) includes an eventual regulatory requirement for a uniform national track-and-trace system for prescription drugs—an interoperable system in which manufacturers and repackagers are required to affix product identifiers to prescription-drug packaging for drug pedigree and monitoring purposes.[50] The passage of this act in the USA represents a domestic-policy response following counterfeit bevacizumab detection, but seems to fall short of establishing sufficient protections.[51] Although track-and-trace technology, if implemented and followed correctly, has the potential to act as an important component of counterfeit-drug surveillance, full implementation of the DSCSA (such as the requirement for tracking medications at the unit level) is nearly a decade away, and the law has limitations. Specifically, the focus of the DSCSA on issuing guidance on specific scenarios that could increase the risk of sourcing illegitimate products might not address the criminal element of the counterfeit-drug trade.[52] Criminals who knowingly sell and purchase counterfeit medicines would be unlikely to report violations, could circumvent the law through countermeasures to track-and-trace and anticounterfeiting technologies, and might use alternative sourcing options that remain largely unregulated.[28,53] Additionally, although the DSCSA requires systems of notification, quarantine, and investigation of suspect and/or illegitimate products by manufacturers and trading partners, more proactive regulatory actions, such as random risk-based testing of drug quality, enhanced penalties and sanctions for criminal violations of the law, and notification of possible safety risks at the patient level, are absent.

Opposition to national track-and-trace legislation by the pharmaceutical industry, citing compliance costs and technical challenges, could represent a major barrier to timely implementation of the DSCSA, and could limit the effectiveness of future FDA guidance.[54,55] Instead, industry stakeholders should recognize the benefits of full DSCSA implementation as one important element in the fight against counterfeit medicines, and should pursue cooperation and coordination (such as establishing uniform parameters and standards) in order to mitigate risk, separate legitimate from criminal elements in the supply chain, and enhance patient safety. This approach could also establish the DSCSA as a model anticounterfeiting strategy, although translation of its obligations would have to be contextualized to different global settings, such as markets in which counterfeit-drug sourcing occurs outside of traditional drug-supply chains, as in rural (for example, Chinese) and informal (for example, Indian) economic sectors.[28,56–58] Other solutions, such as increasing criminal penalties for those involved in the trade, sale, purchase, and use of counterfeit medicines, as in the proposed US Counterfeit Drug Penalty Enhancement Act, should also be seriously considered as complementary legislation to the DSCSA, but could also face opposition.[59]

Specific risk factors associated with the grey market that were prominent in the detection of counterfeit bevacizumab have yet to be adequately addressed. This includes aggressive marketing to US medical clinics of counterfeit versions at deeply discounted prices (up to 60–80% discounts, according to legal filings).[3,13,15,60,61] With an estimated cost per patient of up to $100,000 per year, the popularity and high cost of Avastin® are likely to create continued market opportunity for illegal production and sourcing of counterfeit versions, despite ongoing debate regarding the drug's cost-effectiveness in relation to cancer treatment and survival.[62–64] Depending on the purchase price and the method of reimbursement, hospitals and clinicians in the USA can even lose money when administering Avastin®, so they can be extremely sensitive to pricing of the drug.[63]

A further complication is Genentech's recent decision to limit distribution of Avastin®, and the anticancer drugs Herceptin® (trastuzumab) and Rituxan® (rituximab), through six speciality drug distributors.[65] Although Genentech has cited the counterfeit bevacizumab incident as a reason for its supply-chain modification, critics have argued that this change will lead to delays in treatment, and will increase drug costs for providers and patients.[65] Drug manufacturers should address the underlying problem that leads to market demand for counterfeit versions, which is the general lack of affordability and accessibility to oncology drugs.[66,67] This aim can be accomplished by proactively assessing innovative strategies for pricing and intellectual-property management, such as differential pricing based on ability-to-pay, expanding available prescription patient access and assistance programmes, and out-licensing production to local manufacturers in underserved global markets.[68,69]

Conclusions

The detection of counterfeit bevacizumab in the legitimate and controlled drug-supply chain of the USA is a reflection of the larger pharmaceutical criminal enterprise that profits by the illegal trade of counterfeit medicines at the expense of patient populations all around the world.[5,28] This egregious form of pharmaceutical crime can affect the poorest populations in the least-developed countries, and, as the Avastin® case shows, intensively treated patients in the most-developed countries.[6] Clinicians should be wary, and public health researchers and policymakers should study and prioritize greater understanding of this patient-safety event, to prevent the unethical from profiting from the most vulnerable of groups: patients. Although domestic-policy responses aimed at improving pharmaceutical security are important first steps, renewed international commitment to combating counterfeit medicines is urgently needed in this era of globalized, but complex and vulnerable, drug-supply chains. Domestic and global policy solutions should also prioritize patients with cancer as a group that is particularly susceptible to the dangers of counterfeit medicines. Although some might view the discovery of counterfeit bevacizumab as an isolated incident in the history of US drug safety, we assert that it is in fact a symptom of one of the most serious and underaddressed global public-health challenges that we face in the 21st century, and one that requires immediate and tangible action in order to prevent another counterfeit-drug incident.

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1. US Food and Drug Administration. *Counterfeit Version of Avastin in U. S. Distribution* [online], http://www.fda.gov/drugs/drugsafety/ucm291960.htm (2012).
2. PMGroup, PMLiVE. *Top 50 pharmaceutical products by global sales* [online], http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales (2015).
3. Weaver, C. & Whalen, J. How Fake Cancer Drugs Entered U. S. *The Wall Street Journal* [online], http://online.wsj.com/news/articles/SB10001424052702303879604577410430607090226 (2012).
4. Attaran, A. *et al.* How to achieve international action on falsified and substandard medicines. *BMJ* **345**, e7381 (2012).
5. Mackey, T. K. & Liang, B. A. Improving global health governance to combat counterfeit medicines: a proposal for a UNODC–WHO–Interpol trilateral mechanism. *BMC Med.* **11**, 233 (2013).
6. Mackey, T. K. & Liang, B. A. Oncology and the Internet: regulatory failure and reform. *J. Oncol. Pract.* **8**, 341–343 (2012).
7. Institute for Safe Medication Practices. *Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche During the Drug Shortage Crisis* [online], http://www.ismp.org/Newsletters/acutecare/showarticle.asp?ID=3 (2011).
8. Whalen, J. Egypt Eyed as Possible Source of Fake Avastin. *The Wall Street Journal* [online], http://online.wsj.com/articles/SB10001424052970204880404577229380581802606 (2012).
9. Sandle, P. & Acher, J. Denmark's CareMed says shipped fake Avastin unwittingly. *Reuters* [online], http://www.reuters.com/article/2012/02/17/us-caremed-avastin-idUSTRE81G1S920120217 (2012).
10. US Food and Drug Administration. *Letters to Doctors about Risks of Purchasing Medications from Foreign or Unlicensed Suppliers* [online], http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/ucm330610.htm (2012).
11. Weaver, C., Whalen, J. & Faucon, B. Drug Distributor Is Tied to Imports of Fake Avastin. *The Wall Street Journal* [online], http://www.wsj.com/articles/SB10001424052970203370604577261343974214110 (2012).
12. Kuehn, B. M. FDA warning: new batch of fake bevacizumab found. *JAMA* **309**, 864–864 (2013).
13. US Food and Drug Administration. *August 23, 2012: California Man Sentenced for Importing Adulterated Cancer Drugs; Forfeits $1.4 Million & Land Rover Automobile* [online], http://www.fda.gov/ICECI/CriminalInvestigations/ucm316986.htm (2012).
14. US Food and Drug Administration. *July 11, 2013: English Citizen Sentenced for Distributing Adulterated and Counterfeit Cancer Drugs* [online], http://www.fda.gov/ICECI/CriminalInvestigations/ucm360652.htm (2013).
15. Department of Justice. United States Attorney's Office, Eastern District of Tennessee. *Greeneville Oncologist And Practice Manager Sentenced For Violating Food, Drug And Cosmetic Act: Cancer Clinic Purchased Unapproved Drugs for Three Years* [online], http://www.justice.gov/usao/tne/news/2014/June/061214%20Sen%20Sentencing%20FDA.html (2014).
16. The Federal Bureau of Investigation, Knoxville Division. *Johnson City Physician Sentenced to Serve Two Years in Prison for Violations Related to Unapproved Foreign Drugs* [online], http://www.fbi.gov/knoxville/press-releases/2013/johnson-city-physician-sentenced-to-serve-two-years-in-prison-for-violations-related-to-unapproved-foreign-drugs (2013).
17. Weaver, C. U. S. Fake-Drug Probe Puts Spotlight on Role of Doctors. *The Wall Street Journal* [online], http://online.wsj.com/news/articles/SB10001424127887323353204578129682462065220 (2012).
18. US Food and Drug Administration. *January 16, 2014: Two Turkish Nationals Indicted for Smuggling Counterfeit Cancer Drug* [online], http://www.fda.gov/ICECI/CriminalInvestigations/ucm383001.htm (2014).
19. Whalen, J. Turkish Drug Exporter Ozay Draws U. S. Scrutiny. *The Wall Street Journal* [online], http://online.wsj.com/news/articles/SB10001424052702303546204579435692215579758 (2014).
20. Department of Justice. United States Attorney's Office, Eastern District of New York. *Two Officers Of Long Island Based Company Indicted For Sale.Of $17 Million Worth Of Misbranded Prescription Drugs Including Counterfeit Cancer Drugs* [online], http://www.justice.gov/usao/nye/pr/April14/2014Apr30.php (2014).
21. US Food and Drug Administration. *February 16, 2012: Local Cancer Doctor Pleads Guilty to Receiving Misbranded Cancer Drugs Two Californians also Named in Indictment* [online], http://www.fda.gov/ICECI/CriminalInvestigations/ucm294706.htm (2012).
22. Liang, B. A. & Mackey, T. Searching for safety: addressing search engine, website, and provider accountability for illicit online drug sales. *Am. J. Law Med.* **35**, 125–184 (2009).
23. Institute of Medicine. *Countering the Problem of Falsified and Substandard Drugs* [online], http://www.iom.edu/Reports/2013/Countering-the-Problem-of-Falsified-and-Substandard-Drugs.aspx (2013).
24. Qureshi, Z. P *et al.* Caveat Oncologist: clinical findings and consequences of distributing counterfeit erythropoietin in the United States. *J. Oncol. Pract.* **8**, 84–90 (2012).
25. Sun, X., Xu, X. & Zhang, X. Counterfeit bevacizumab and endophthalmitis. *N. Engl. J. Med.* **365**, 378–379 (2011).
26. Garcia-Aguirre, G., Vanzinni-Zago, V. & Quiroz-Mercado, H. Growth of Scytalidium sp. in a counterfeit bevacizumab bottle. *Indian J. Ophthalmol.* **61**, 523–525 (2013).

27. Wang, F. *et al.* Acute intraocular inflammation caused by endotoxin after intravitreal injection of counterfeit bevacizumab in Shanghai, China. *Ophthalmology* **120**, 355–361 (2013).
28. Mackey, T. K. & Liang, B. A. The global counterfeit drug trade: patient safety and public health risks. *J. Pharm. Sci.* **100**, 4571–4579 (2011).
29. Almuzaini, T., Sammons, H. & Choonara, I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open* **3**, e002924 (2013).
30. Gostin, L. O., Buckley, G. J. & Kelley, P. W. Stemming the global trade in falsified and substandard medicines. *JAMA* **309**, 1693–1694 (2013).
31. Karunamoorthi, K. The counterfeit anti-malarial is a crime against humanity: a systematic review of the scientific evidence. *Malar. J.* **13**, 209 (2014).
32. Newton, P. N., Green, M. D. & Fernández, F. M. Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol. Sci.* **31**, 99–101 (2010).
33. Nayyar, G. M., Breman, J. G., Newton, P. N. & Herrington, J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect. Dis.* **12**, 488–496 (2012).
34. Mackey, T. K. Global health diplomacy and the governance of counterfeit medicines: a mapping exercise of institutional approaches. *Journal of Health Diplomacy* [online], http://www.ghd-net.org/sites/default/files/Global%20Health%20Diplomacy%20and%20the%20Governance%20of%20Counterfeit%20Medicines.pdf (2013).
35. Rosenthal, E. T. The 'gray market' raises concerns about cost, safety, and ethics. *J. Natl Cancer Inst.* **104**, 168–170 (2012).
36. Woodward, C. Prices gone wild: grey market 'scalpers' scoring windfall in American drug market. *CMAJ* **184**, E119–E120 (2012).
37. Forman, R. F. Availability of opioids on the Internet. *JAMA* **290**, 889 (2003).
38. Liang, B. A. & Mackey, T. K. Online availability and safety of drugs in shortage: a descriptive study of internet vendor characteristics. *J. Med. Internet Res.* **14**, e27 (2012).
39. Liang, B. A. & Mackey, T. K. Vaccine shortages and suspect online pharmacy sellers. *Vaccine* **30**, 105–108 (2012).
40. Mackey, T. K., Liang, B. A. & Strathdee, S. A. Digital social media, youth, and nonmedical use of prescription drugs: the need for reform. *J. Med. Internet Res.* **15**, e143 (2013).
41. Orizio, G. *et al.* 'Save 30% if you buy today'. Online pharmacies and the enhancement of peripheral thinking in consumers. *Pharmacoepidemiol. Drug Saf.* **19**, 970–976 (2010).
42. CBC News. *Canadadrugs.com's wholesale licence suspended* [online], http://www.cbc.ca/1.2669583 (2014).
43. Mackey, T. K. & Liang, B. A. Pharmaceutical digital marketing and governance: illicit actors and challenges to global patient safety and public health. *Global Health* **9**, 45 (2013).
44. Brookings Institute. *Reducing the Threat of Counterfeit and Unapproved Drugs in Clinical Settings* [online], http://www.brookings.edu/events/2013/07/19-counterfeit-unapproved-drugs-threat (2013).
45. Crinò, L. *et al.* Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. *Lancet Oncol.* **11**, 733–740 (2010).
46. Hurwitz, H. & Saini, S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin. Oncol.* **33**, S26–S34 (2006).
47. Saif, M. W. Managing bevacizumab-related toxicities in patients with colorectal cancer. *J. Support. Oncol.* **7**, 245–251 (2009).
48. Hershman, D. L. *et al.* Contraindicated use of bevacizumab and toxicity in elderly patients with cancer. *J. Clin. Oncol.* **31**, 3592–3599 (2013).
49. Moisee, K. Cancer Patients Furious Over Counterfeit Avastin. *ABC News* [online], http://abcnews.go.com/Health/CancerPreventionAndTreatment/cancer-patients-furious-counterfeit-avastin/story?id=15629540 (2012).
50. US Food and Drug Administration. *Drug Supply Chain Security Act (DSCSA)* [online], http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ (2013).
51. Outterson, K. The Drug Quality and Security Act—mind the gaps. *N. Engl. J. Med.* **370**, 97–99 (2014).
52. US Food and Drug Administration. *Guidance for Industry: Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification* [online], http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf (2014).
53. Bansal, D., Malla, S., Gudala, K. & Tiwari, P. Anti-counterfeit technologies: a pharmaceutical industry perspective. *Sci. Pharm.* **81**, 1–13 (2013).
54. Yukhananov, A. Congress fails to agree on national drug trace plan. *Reuters* [online], http://www.reuters.com/article/2012/06/18/us-congress-fda-trace-idUSBRE85H1QF20120618 (2012).
55. Barlas, S. Track-and-trace drug verification: FDA plans new national standards, pharmacies tread with trepidation. *PT* **36**, 203–231 (2011).
56. Mackey, T. K. & Liang, B. A. Combating healthcare corruption and fraud with improved global health governance. *BMC Int. Health Hum. Rights* **12**, 23 (2012).
57. Yip, W. & Mahal, A. The health care systems of China and India: performance and future challenges. *Health Affairs* **27**, 921–932 (2008).
58. Gautam, C. S., Utreja, A. & Singal, G. L. Spurious and counterfeit drugs: a growing industry in the developing world. *Postgrad. Med. J.* **85**, 251–256 (2009).
59. Congressman Patrick Meehan, Representing the 7th District of Pennsylvania. *Meehan Bill to Crackdown on Counterfeit Rx Drug Trafficking Passes House* [online], http://meehan.house.gov/latest-news/meehan-bill-to-crackdown-on-counterfeit-rx-drug-trafficking-passes-house/ (2012).
60. [No authors listed] Shortages of cancer drugs in the USA. *Lancet Oncol.* **12**, 313 (2011).
61. Gatesman, M. L. & Smith, T. J. The shortage of essential chemotherapy drugs in the United States. *N. Engl. J. Med.* **365**, 1653–1655 (2011).
62. Montero, A. J. & Vogel, C. Fighting fire with fire: rekindling the bevacizumab debate. *N. Engl. J. Med.* **366**, 374–375 (2012).
63. Kolata, G. & Pollack, A. The Evidence Gap: Costly Cancer Drug Offers Hope, but Also a Dilemma. *The New York Times* [online], http://www.nytimes.com/2008/07/06/health/06avastin.html?pagewanted=all&_r=0 (2008).
64. Jirillo, A., Vascon, F. & Giacobbo, M. Bevacizumab in advanced cancer, too much or too little? *Ann. Oncol.* **19**, 1817–1818 (2008).
65. Berkrot, B. Roche's Genentech defends supply shift for top cancer drugs. *Yahoo Finance* [online], http://finance.yahoo.com/news/roches-genentech-defends-supply-shift-233532371.html (2014).
66. Kelly, R. J. & Smith, T. J. Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care. *Lancet Oncol.* **15**, e112–e118 (2014).
67. Mileshkin, L. & Sullivan, D. Access to expensive anti-cancer drugs. *J. Law Med.* **19**, 232–243 (2011).
68. Essential Medicines and Health Products Information Portal. *Promoting Access to Medical Technologies and Innovation. Intersections Between Public Health, Intellectual Property and Trade* [online], http://apps.who.int/medicinedocs/en/d/Js20030en/ (2013).
69. Mackey, T. K. & Liang, B. A. Promoting global health: utilizing WHO to integrate public health, innovation and intellectual property. *Drug Discov. Today* **17**, 1254–1257 (2012).

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