Reforming direct-to-consumer advertising

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Why not exploit direct-to-consumer advertising to facilitate patient education about treatments and improve safety monitoring?

Direct-to-consumer (DTC) advertising is the fastest growing form of drug marketing with a global reach, despite being legal only in the United States and New Zealand. One goal of DTC advertising is to provide consumers with information about marketed drugs, but its use is also correlated with an increase in drug expenditures, the overutilization of brand name drugs, misleading or false forms, and patient safety risks. Although industry spending on DTC advertising has continued to skyrocket, regulatory efforts focusing on the marketing practice have languished. Simultaneously, no incentives exist for drugmakers to provide information to at-risk, underserved groups. US legislative efforts to ban or limit DTC advertising have been unsuccessful. The US Food and Drug Administration (FDA) has recently begun a re-evaluation of its DTC advertising regulatory approach. It is our view that the FDA should transform DTC advertising oversight so that it can be exploited to provide treatment information to at-risk populations, disseminate disclosures on comparative effectiveness and dovetail with patient safety communications. Incorporation of such information into DTC advertising could be relatively straightforward by building on existing regulations. Here we assess US efforts to regulate DTC advertising and then propose changes that would promote better patient information and safety communications.

The rise of DTC advertising

Following the liberalization of advertising guidelines by the FDA 14 years ago, patients exposed to television, magazines or the internet have been increasingly subjected to DTC advertising. In addition to providing information about marketed drugs, DTC advertising is often viewed as a means of bypassing physicians and influencing patients to ask for specifically advertised drugs[1].

From the drug industry's perspective, DTC advertising has been very successful, with 91% of US adults having seen or heard such advertisements[2]. But concerns have been raised on how to address the proliferation of DTC advertising and in particular its focus on expanding the markets to ever-greater numbers of patients, irrespective of a drug's efficacy in a particular indication in very large, heterogeneous patient groups[3,4]. In response to these concerns, the FDA has announced plans for regulatory reform[5].

DTC advertising could be argued to be especially important for the marketing of biotech products, given their high development costs and scientific complexity[6]. Biotech firms may need to leverage DTC advertising to recoup R&D costs, while also adequately communicating the risk and benefits of complex biologics using cost-effective and targeted DTC advertising, such as marketing online[6].

Only the United States and New Zealand currently allow DTC advertising. Other countries reject this form of marketing. For example, European Union legislation that would have allowed only limited forms of DTC advertising was soundly defeated in 2009 (ref. 7). Yet DTC advertising has become a staple of pharmaceutical marketing in the United States. With over $4 billion dollars in US expenditures in 2009 (**Fig. 1**), DTC advertising has grown twice as fast as all other forms of promotion (including promotion to physicians) as well as the amount spent by companies on R&D[8]. From 1996 to 2005, spending on DTC advertising increased by 330%[9]. Increased DTC advertising expenditures have led to increases in prescription drug use[8]. Studies have shown that for every $1 spent on DTC advertising, $2.20–4.20 of sales are generated[8,10].

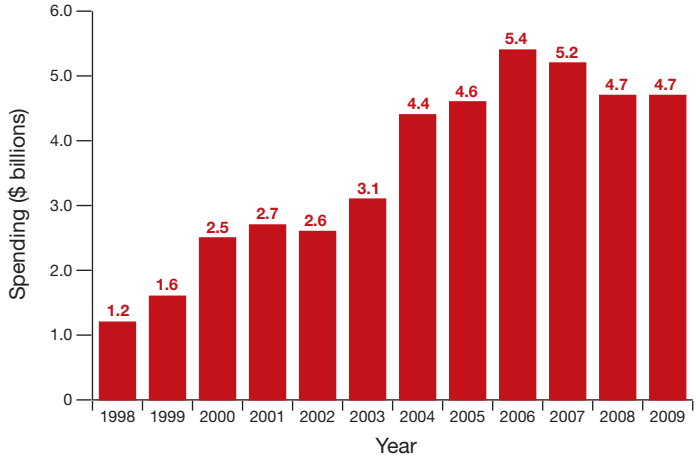

Figure 1 A decade of DTC advertising in the United States. Spending has increased over fourfold since 1998. Source: TNS Media Intelligence and *The Wall Street Journal*.

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Furthermore, despite legal efforts, the impact of DTC advertising may spill across geopolitical lines. Studies show that US DTC advertising may have adverse public health consequences in countries where such forms of advertising are not permitted. For example, cross-border advertising resulted in increased prescribing of tegaserod (sold as Zelnorm) in Canada; the drug was later removed from the market over safety concerns[11]. Similarly, observers in both Australia and Europe have identified the potential negative consequences of cross-border DTC advertising and have indicated that domestic DTC advertising bans may be insufficient[12,13]. Indeed, DTC advertising represents a global challenge, with concerns regarding how to appropriately regulate US and New Zealand DTC advertising disseminated by satellite TV, online ads and websites, sponsored links on search engines and social media, as well as print, which are similarly not limited to geopolitical boundaries[3].

Critics argue information provided by DTC advertising has limited educational benefit for patients, and may be inaccurate or misleading[1]. Little information is given on medical costs, risk factors or populations that may benefit from treatment whereas drug benefits are overstated and the impact of healthy lifestyles minimized[14]. Analysis also suggests that DTC advertising may result in inappropriate physician prescribing practices, unnecessary visits and may adversely affect the physician-patient relationship[15]. DTC advertising has also been linked to the growing escalation of healthcare costs through increased prescription drug spending and utilization of advertised drugs[9].

Critics further point out that DTC advertising has not been effective in presenting drug risks and benefits and is particularly problematic in informing patients about risk profiles of complex drugs, such as biologics[6]. Indeed, DTC advertising marketing of biologics has been characterized as ineffective because many biologic drug programs require targeted therapy marketing focused on smaller populations and an emphasis on science and detailed patient education—attributes not conducive to current industry DTC advertising approaches[6].

Risky marketing for patients

Importantly, most DTC advertising campaigns begin early in the product life cycle. They frequently focus on blockbuster and lifestyle drugs that have limited drug patient safety experience and postmarket surveillance[9]. But this focus on blockbuster and lifestyle drugs excludes provision of information to traditionally ignored at-risk groups, such as pediatric patients, pregnant women and orphan disease patients. Furthermore, the 2004 withdrawal of Merck's (Whitehouse Station, NJ, USA) Vioxx (rofecoxib) illustrates the risk of how aggressive DTC advertising can increase the likelihood of a drug being prescribed beyond that drug's labeled indication and against a background where information about that drug's safety profile is limited at best[16].

In response to these concerns, the drug industry association Pharmaceutical Research and Manufacturers of America adopted voluntary guidelines encouraging companies to educate physicians and patients before they commence their first DTC advertising campaigns[16]. Even so, US legislators have noted that the voluntary guidelines, which do not define a specific time frame for commencing DTC advertising, are insufficient and have advocated more stringent legislation[16]. Indeed, self-regulation by industry seems inadequate. Since 2004, drug companies have paid a total of $7 billion dollars in fines and penalties for inappropriate advertising, including the largest criminal fine in US history ($1.2 billion) paid by Pfizer in 2009. These fines were mostly for illegal off-label promotion of its products, which includes the use of DTC advertising[17].

Limited DTC advertising regulation effectiveness

The FDA regulates the promotional labeling and advertising of prescription drugs through its Division of Drug Marketing, Advertising and Communications (DDMAC). DDMAC reviews advertising and promotional materials for false or misleading claims, including assessment of voluntary prerelease draft submittals from drug companies by advisory review, and through postrelease regulatory letters to compel specific remedial action (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm). At the moment, however, there is no requirement for DTC advertising prerelease approval by FDA; indeed, the lack of detailed FDA guidance on how to appropriately present such information has made it difficult for firms to assess whether they are in compliance with FDA regulations[5]. Yet even as DTC advertising has grown, an alarming reduction in issued regulatory letters, lack of adequate staff for advertisement review, and a decline in the number of advertisements that underwent FDA review before airing has occurred[9]. At present, there are no incentives for drug companies to fill information vacuums for education regarding complex drugs and/or at-risk populations.

In addition, even when the FDA has regulated the practice, the US Government Accountability Office reported that the agency only reviewed a small percentage of received DTC advertising materials, issued regulatory letters that were late and ineffective in preventing dissemination of inappropriate materials, and was unable to track and identify high-priority DTC advertisements[8]. This situation is further exacerbated by overarching concerns regarding FDA's weakness in oversight of postmarket surveillance of drug safety[18]. Commentators have noted that revisiting current DTC advertising rules is necessary to improve FDA's regulatory oversight[4].

US legislative efforts

With the limited ability of the FDA to monitor and proactively regulate questionable forms of DTC advertising, US lawmakers have taken notice but have failed to pass legislation limiting or prohibiting DTC advertising[19]. One controversial proposal would have established a ban or temporary moratorium on DTC advertising for new products, consistent with an Institute of Medicine of the National Academies report calling for both specific warnings and a two-year moratorium on DTC advertising after new drug approval[20]. Two companies, Bristol-Myers Squibb (Princeton, NJ, USA) and Pfizer (New York), voluntarily adopted postapproval moratoriums, albeit shorter ones, of a year or six months, respectively, before starting DTC advertising campaigns[20]. A limited ban has also been proposed by Rep. Henry Waxman (D-CA), who favors granting FDA authority to prohibit DTC advertising for an initial period after a new drug is approved, on a case-by-case basis[19].

Even so, any actual US ban would likely fail in the courts and could pose a risk for future regulation of DTC advertising[20]. Indeed, past attempts aimed at establishing a temporary DTC advertising moratorium in 2007 by the US Congress failed to become law owing to concerns regarding constitutional protection of commercial free speech[4]. Such concerns are analogous to rulings striking down the FDA's ability to limit off-label promotion of pharmaceuticals, and indicate that a full DTC advertising ban would likely be unsuccessful[20].

Reform

FDA's announced DTC advertising regulatory reform efforts, which include DDMAC reorganization, an amendment of regulations concerning 'fair balance' provisions of clarity, neutrality and risk information presented in DTC advertising, and expanded resources available for this effort provides a window of opportunity for reform[5]. Given the limited effectiveness of current regulatory regimes and legal unlikelihood of DTC advertising prohibition, DTC advertising rules should focus on strategies to both improve current

DTC advertising regulatory approaches and enhance the value and effectiveness of existing DTC advertising content. Regulatory systems can be improved by taking advantage of extensive DTC advertising dissemination to provide targeted drug information to at-risk patient populations and by its integration into a safety communications system. The quality of DTC advertising could also be enhanced by requiring disclosure of comparative analysis. These efforts are consistent with current US regulations, including those of fair balance reporting of advertised information.

Targeted DTC advertising for at-risk patient populations

Regulatory reform exploiting targeted DTC advertising could act as an effective education and communication tool for certain at-risk populations that currently receive limited treatment information[21]. In addition, appropriate DTC advertising that presents information fairly and truthfully in accordance with current regulations could be used as an aid for public health purposes.

Such targeted DTC advertising could be incentivized by FDA fast-track review and user fee discounts for DTC advertising aimed at certain at-risk populations, identified by the FDA, who receive limited marketing attention, including pediatric patients, pregnant women and individuals suffering from orphan diseases, as well as those who would benefit from advertisements for public health intervention products, such as smoking cessation. This proposal would be similar to those that address identified provider ignorance by allowing limited off-label promotion for certain orphan disease drug treatments under additional FDA oversight using a special FDA enrollment application and a risk management and pharmacovigilance plan for drug study and monitoring[21]. Such a process could also lead to increasing utilization of biotech drugs for new indications and take advantage of the growing industry attention to underserved, at-risk populations[22]. Such a complementary approach could motivate manufacturers to provide information to at-risk patients (as well as their physicians) on available treatments and promote public health.

Patient safety information

Beyond expanding information flow to at-risk groups, regulation of DTC advertising should also be expanded for proactive use in safety communications, such as informing patients about adverse drug events and product corrections and/or recalls. This can be accomplished by requiring manufacturers to submit a detailed plan for a comprehensive safety information dissemination campaign, using both traditional (TV advertisements, radio and print) and online (online advertising, social media sites and mobile) forms of DTC advertising to proactively communicate to their consumers in the event of a safety or adverse event involving their products. Implementation of this DTC advertising communication plan could be done in conjunction with existing risk evaluation and mitigation strategies (REMS) currently required by the FDA to market certain products[23]. This would include the requirement that manufacturers add a component of DTC advertising safety communication during REMS assessment of an unapproved pharmaceutical or in the event the FDA becomes aware of adverse safety information regarding a marketed product[23]. Guidance encouraging DTC advertising communication in voluntary REMS compliance by the industry would further ensure that safety communication reached both physicians and patients.

Currently, FDA maintains the MedWatch online database (http://www.fda.gov/Safety/MedWatch/default.htm) to inform the public and clinicians about safety information and adverse drug events[24]. Yet its effectiveness as a vehicle for capturing and communicating information to patients is questionable[25]. By extending safety and adverse event information directly to consumers through the highly disseminated DTC advertising process, patients would have better and more timely access to potentially lifesaving information about drugs.

This combined approach would integrate DTC advertising into a public safety notification system for postmarket surveillance and would require manufacturers to present such adverse event information in a fair and balanced manner. This 'reverse' notification system has already been successfully used in the United States, with regulators requiring corrective television and print advertisement campaigns for misleading advertising of Bayer's best-selling oral contraceptive Yaz (drospirenone and ethinyl estradiol)[19]. Thus, this expanded safety effort would build on those already required under statutory obligations of adverse event reporting for marketed drugs[24].

In addition, the combination of DTC advertising safety communications coupled with an FDA link to refined MedWatch data in online searches could make such information more accessible and potentially consumer friendly[3]. Although implementing such a system would not be without cost, it would provide consumers with immediate access to the reliable, science-based information needed to make more informed decisions about which drugs to consider discussing with their physicians and when to potentially discuss discontinuing drug use (in the light of safety information).

Comparative analysis disclosures

Finally, to increase transparency regarding the risks of drugs portrayed in DTC advertising, drug manufacturers should also disclose all material information that allows a meaningful comparison to existing therapies, potentially more cost and clinically effective, as a condition of approved DTC advertising. This improvement in the value of DTC advertising for patients could include disclosure of clinical trial comparisons to placebo, positive and negative data, as well as future comparative effectiveness work under US healthcare reform. The disclosure requirement could act as an incentive for manufacturers to invest in comparative effectiveness research to use DTC advertising to market their product. This requirement is consistent with the recent US policy efforts to emphasize comparative effectiveness research (http://www.hhs.gov/recovery/programs/cer/index.html).

Other reform proposals, such as requiring DTC advertising to facilitate identification of appropriate patient candidates for treatment, inclusion of accurate and specific quantitative benefit and risk data, use of a 'drug facts box' to educate consumers, and ensuring that DTC advertising information can be easily understood by most consumers, could also be integrated into this disclosure[15,26]. Though observers have expressed reservations regarding the effectiveness of disclosure alone, particularly in disclosure of individual financial conflicts of interest in the medical setting, the combination of reforms explored in this discussion, including disclosure, could provide a comprehensive, more effective approach in protecting patients[27]. Furthermore, beyond static disclosure, disclosure should also be dynamic, with updates on findings related to the drug through amended DTC advertisements.

Conclusions

DTC advertising represents the fastest growing form of pharmaceutical marketing and has a global reach. Drug manufacturers, including biotech firms, will increasingly invest in new technology and marketing strategies to leverage this form of communication directly to patients. Yet DTC advertising has been criticized for its focus on blockbuster, lifestyle drugs and ignoring the needs of at-risk, underserved patients. Given the limited effectiveness of current FDA efforts regarding US DTC advertising and the legal difficulty of implementing a DTC advertising ban, a different approach may be more fruitful.

By encouraging fair and balanced education of complex therapies needed by at-risk populations, increased, dynamic data and comparative effectiveness disclosure and the integration of patient safety data, DTC advertising may serve as a vehicle for more effective, appropriate information dissemination to patients.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Wolfe, S. *N. Engl. J. Med.* **346**, 524–526 (2002).
2. http://www.kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=14378
3. Kuehn, B. *J. Am. Med. Assoc.* **303**, 311–313 (2010).
4. Lurie, P. *J. Law Med. Ethics* **37**, 444–450 (2009).
5. http://edocket.access.gpo.gov/2010/pdf/2010-6996.pdf
6. Mack, J. *Nat. Biotechnol.* **24**, 267 (2006).
7. Anonymous. *Bulletin of the World Health Organization.* **87** (2009). <http://www.who.int/bulletin/volumes/87/8/09-040809/en/index.html>
8. Anonymous. *Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising.* i-48 (US Government Accountability Office, Washington, DC, 2006). <http://www.gao.gov/new.items/d0754.pdf>.
9. Donohue, J.M., Cevasco, M. & Rosenthal, M.B. *N. Engl. J. Med.* **357**, 673–681 (2007).
10. Anonymous. *Impact of Direct-to-Consumer Advertising on Prescription Drug Spending* (The Henry J. Kaiser Family Foundation, 2003). <http://www.kff.org/rxdrugs/upload/Impact-of-Direct-to-Consumer-Advertising-on-Prescription-Drug-Spending-Summary-of-Findings.pdf>.
11. Law, M. *et al. Br. Med. J.* **337**, a1055 (2008).
12. Mackenzie, F.J. *et al. Intern. Med. J.* **37**, 224–228 (2007).
13. Velo, G. & Moretti, U. *Br. J. Clin. Pharmacol.* **66**, 626–628 (2008).
14. Frosch, D.L. *et al. Ann. Fam. Med.* **5**, 6–13 (2007).
15. Frosch, D.L. *et al. Am. J. Public Health* **100**, 24–32 (2010).
16. Vastag, B. *Nat. Biotechnol.* **25**, 267 (2007).
17. Evans, D. Pfizer broke the law by promoting drugs for unapproved uses. *Bloomberg* (9 November 2009). <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yV1nYxCGoA>.
18. Anonymous. *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed.* i-49 (US Government Accountability Office, Washington, DC, 2009).
19. Singer, N. Lawmakers seek to curb drug commercials. *New York Times* (27 July 2009). <http://www.nytimes.com/2009/07/27/business/media/27drugads.html?_r=1&ref=health>.
20. Shuchman, M. *N. Engl. J. Med.* **356**, 2236–2239 (2007).
21. Liang, B.A. & Mackey, T. *Science* **327**, 273–274 (2010).
22. http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3426.
23. Anonymous. *Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modification.* (US HHS, FDA, CDER, CBER, 2009) <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.
24. 21 CFR 310.305.
25. Couzin, J. *Science* **307**, 196–198 (2005).
26. Woloshin, S., Schwartz, L. & Welch, H. *Health Aff.* **W4**, 234–245 (2004).
27. Rodwin, M.A. *N. Engl. J. Med.* **321**, 1405–1408 (1989).