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The Wider Use of Fixed-Dose Combinations Emphasizes the Need for a Global Approach to Regulatory Guideline Development

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Abstract

A fixed-dose combination (FDC) is a drug product in which two or more separate drug components (active pharmaceutical ingredients) are combined in a single-dosage form. Interest in developing FDCs is increasing in a range of diseases. This project investigated the regulatory environment for FDCs in the EU and US. A review of the FDC guidelines set forth by the EMA, FDA, and ICH, followed by interviews of key informants in industry, identified 5 main industry concerns related to development of FDCs. These concerns were presented to key informants from both the EU and US regulatory authorities. It was clear from the results that the current regulatory environment for FDCs lacks consistency. This may create a barrier to innovation moving from the laboratory to the clinic, as companies cannot clearly see the development path requirements. This project also highlighted certain challenges that currently face the regulatory world: how to improve the role of regulatory science and provide clear quantification in assessment decisions; the role of guidelines and their impact on innovation; and, most important, the question of globalization and how to move toward a more harmonized regulatory system.

Keywords

fixed-dose combination, guidelines, drug, medicine, development, innovation, regulatory science, global

Introduction

The understanding of the complexity of the disease process and our ability to describe that complexity—the approach of systems biology—has developed rapidly in recent years and is gaining attention. The ''one drug/one disease target'' philosophy (monotherapy), which has dominated drug development and medical treatment for the past few decades, is no longer considered sufficient for a growing range of disease indications. For such complex diseases as HIV/AIDS, cancer, hypertension, diabetes, and cardiovascular diseases, monotherapy is clearly not optimal. The burden of these types of disease, which are often chronic, is increasing rapidly in societies around the world, due to aging populations and lifestyle factors.[1] Combination therapy for such diseases—treatment using more than one separate drug—is common in clinical practice, even though there is often limited safety and efficacy information on such combinations. Fixed-dose combinations (FDCs) provide a clinically tested and dose-adjusted safe format for combination therapy. An increasing realization of this by stakeholders has meant that the development of drugs in combination is coming back onto the agenda. After a decline since the 1970s caused by regulatory intervention, the marketed number of FDCs is increasing.[2] For example, on the Danish market, the total number of authorized FDCs increased 29% from 2010 to 2013 (Vana and Bjerrum, unpublished data, 2014). The hope is that FDCs will encourage new methods to treat diseases more efficiently, provide new opportunities for industry by stimulating innovative approaches to drug discovery and development, replenish product pipelines, and perhaps reduce drug development timelines and costs. This project investigated the

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Table 1. Definitions of the types of FDCs and the terminology used by the EMA, FDA, and ICH.[a]

EMA (2008)	FDA (2006)	ICH (2009)	Terminology Adopted
(a) FDC already approved as free combination therapy; (b) FDC of approved compounds, not approved as free combination therapy	Two or more previously marketed drugs (includes biologics)	Two or more late-stage entities	Category A: Two or more authorized drugs: AD + AD
New active substance plus approved/ well-known compound	New molecular entity plus marketed drug	Late-stage entity plus early-stage entity	Category B: Authorized drug + new investigational drug: AD + NID
Combination of two or more new active substances	New molecular entity plus new molecular entity	Early-stage entity plus early-stage entity	Category C: New investigational drug + new investigational drug NID + NID

Definitions of terminology: *FDC* = fixed-dose combination; *free combination therapy* = two or more drugs in separate formulations, each taken usually at the same time; *new active substance* = an active substance used for the first time in a medicinal product, for either human or veterinary use, equivalent to the FDA term "new molecular entity"; *new molecular entity* = FDA term for an active ingredient that has never before been authorized in the United States in any form; *late-stage entity* = compound with significant phase III or postmarketing clinical experience; *early-stage entity* = compound with limited clinical experience, phase II or less; *authorized drug (AD)* = drug approved for marketing by a recognized regulatory authority; *new investigational drug (NID)* = drug that has not been previously developed for any indication.

[a]A simplified terminology is suggested in the last column as well as by category.

regulatory environment for FDCs in the EU and US to clarify the challenges that face the regulatory authorities in adapting current regulatory approaches and guidelines to enable such opportunities while ensuring rational combinations and patient safety.

Terminology

The terminology related to medicine combinations can be confusing. *Fixed-dose combination* is a term used by the US Food and Drug Administration (FDA) and is defined as "a drug product in which two or more separate drug components (active pharmaceutical ingredients) are combined in a single dosage form."[3] The FDA also uses a second term, *combination product*, defined as "a product comprised of two or more regulated components, ie drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity."[4] Combination products consist of 2 or more types of entities, so the term includes FDCs of drug/biologic but does not include other FDCs, combining drug/drug or biologic/biologic. The FDA's combination product guidelines are aimed at combinations that include a device, not combinations of active ingredients, which are dealt with by FDA guidelines on "combinations."

The European Medicines Agency (EMA) uses the term *fixed combination medicinal product* to refer to an FDC, mixing the words used in the two different terms from the FDA. A lack of any comprehensive glossary covering these terms can lead to considerable initial confusion. To add to this, the term *combination therapy* is commonly used as an umbrella term, including FDCs where dosage is fixed and free combinations where dosage is not fixed.[5] This project focused on and used the terminology *fixed-dose combination* as defined by the FDA.[3]

FDCs are generally divided into categories, depending on whether the active ingredients have been previously authorized or are in late-stage clinical development. Once again, each authority, as well as the International Conference on Harmonisation (ICH), uses it own terminology for the subdivision. Table 1 aligns the different subdivisions. The FDCs for categories A, B, and C are defined, and the terminology suggested in the final column adopted for this project.

Materials and Methods

Key informant interviews—the interviewing of key stakeholders in the field of interest—is a recognized method used to obtain detailed information on a particular subject in a short time.[6]

Key informants from industry were identified by locating companies involved in developing FDCs and identifying employees directly responsible for FDC development or regulation. A total of 8 key industry informants were interviewed, 7 from companies in Denmark and 1 from the UK. Key informants from the EU and US authorities were identified through network connections to regulators and former regulators who had direct experience in the authorization of FDCs. A total of 6 key regulator informants were interviewed: 3 from the EU and 3 from the US. One of the EU regulator informants had recently retired, and 2 of the US regulator informants had moved to working in industry over the previous 5 years.

The interviews were based on 2 questionnaires: the first for industry and the second for the regulator informants. For the industry questionnaire, guidelines relevant for FDCs issued by the FDA, EMA, and ICH were first reviewed. Inconsistencies or gaps in the information were identified, and the questionnaire based on those gaps. Following the industry interviews and analysis of the results, the guideline gaps that were identified as

Table 2. General guidelines available on the 3 categories of fixed-dose combinations.

Guidelines	Category A: AD + AD	Category B: AD + NID	Category C: NID + NID
Nonclinical			
EMA	Guideline on the nonclinical development of fixed combinations of medicinal products[5]		
FDA	Nonclinical safety evaluation of drug or biologic combinations[3]		
ICH	ICH Topic M3(R2) note for guidance on nonclinical safety studies[42]		
Clinical			
EMA	Guideline on the clinical development of fixed combination medicinal products[14]		—
FDA	—	—	Codevelopment of two or more new investigational drugs for use in combination[8]
ICH	—	—	—

AD, authorized drug; NID, new investigational drug.

Table 3. Opinions of the regulatory authority key informants—including 3 from the EU and 3 from the US—regarding the 5 main industry concerns.

	Considered Important by Regulatory Authorities?		
Industry Concern	Yes	No	Unclear
1: There is a need for definitions/glossary at the national level and perhaps, ultimately, ICH harmonization.	++/++	+/+	
2: There is a need for better harmonization between the FDA and EMA guidelines at the clinical level. An ICH guideline is the desired ultimate aim.	+/+	++/++	
3: Clearer information is required regarding the relative importance of different justifications for category A and B FDCs, in particular, convenience/compliance as a rationale.	+++	+++	
4: There is some confusion over the therapeutic area guidelines—is there a need for information on FDCs in more disease areas?	++/+	++	+
5: There is a lack of information related to biopharmaceuticals and parenteral formulations in the EMA clinical guidelines.	++	+	+/++

+ = EU regulatory authority key informant;
+ = US regulatory authority key informant; FDC, fixed-dose combination.

being of major concern to those in industry formed the basis of the second questionnaire for the regulator informants.

Following each interview, the analysis included transcription; summary of the main observations, their implications, and key insights; and a comparison of each question, highlighting commonalities and differences.[7]

Results

In total, there are 5 guidelines available from the EMA, FDA, and ICH that provide general guidance on the development of FDCs. Table 2 gives an overview of the information provided in these guidelines, using the 3 FDC categories defined in Table 1. It appears that, at the nonclinical level, each regulatory body and the ICH provide a relevant and comprehensive nonclinical guideline. At the clinical level, however, the EMA guideline provides information on only category A and B combinations, the FDA on only category C combinations, and there is no ICH guideline. Also reviewed was some additional guidance on clinical FDC development found in the disease-related (therapeutic area) guidelines available from the EMA, FDA, or ICH (E12).

The review of the guidelines identified 7 gaps in the nonclinical and clinical information provided. Following the industry interviews, 5 main industry concerns were formulated. These concerns and a summary of the response by the regulatory informants are provided in Table 3.

Discussion

Each key informant had more than 10 years of experience working with regulatory issues and guidelines. However, those years of experience led to an easier acceptance of certain aspects of the regulatory environment that, to someone coming in fresh to the area, appeared to be an important source of problems—in particular, terminology and the need for global harmonization. It is evident from Table 3 that the regulatory authority informants had differing opinions on most concerns

raised by industry. Only point 3—regarding the clarity of the importance of different justifications for category A and B FDCs—showed a clear division between EU and US perspectives. This is also reflected in the availability of guidelines for these categories (Table 2). The following discussion considers the responses to each point in Table 3.

Concern 1: Terminology—A Need for Clear Definitions and Glossaries

The issue of terminology represents an area that the key informants in general had not given a lot of thought. However, the importance of a clear terminology became evident during the interviews, as even the term *fixed-dose combination* was interpreted differently by each informant. Terminology is the first and biggest problem for a freshman reading the guidelines: the clear meaning of the words is vital for understanding and interpretation, and glossaries are lacking, difficult to locate, or incomplete. The recent emphasis on regulatory science by both the EMA and the FDA may encourage clear definitions and their collection into readily available glossaries. A harmonized glossary at the global level would be difficult, but the majority agreed that a comprehensive glossary from each authority would be helpful and that more harmonized and consistent terminology among authorities would make communication simpler.

Concern 2: The Need for Better Harmonization Between the FDA and EMA Guidelines

Although the majority of regulators in both the EU and the US did not consider harmonization of guidelines among authorities an important issue, in industry there was a real desire to have comprehensive and compatible clinical guidelines available. Currently, if only one authority has issued relevant information on a particular issue, those principles are used as a basis for development outside that authority's jurisdiction, but direct information from an authority would be preferred.

In fact, the absence of an EMA clinical guideline on FDCs of two new chemical entities (category C; Table 2) appears to have been a barrier to larger companies in the EU seriously considering such development, as a majority of the informants from the EU were unaware of this option or at least considered it an unsafe path. This FDA codevelopment path[8] is seen as leading the way in promoting new approaches to combination drug development, including FDCs. Before the release of this guideline, the FDA required that each component of a combination be fully characterized at the clinical level.[9] This had led to any FDC including a novel component always being combined with prior standards of care. The development path for completely novel combinations (category C) is seen to be having a big impact on drug development in the US for infectious diseases and cancer.[10,11] As the guideline is also applicable to other therapeutic areas, an eventual broader impact may be expected.

The recent release of a concept paper by the EMA on the need to revise the guideline on the clinical development of FDCs[12] is encouraging, as it indicates that FDCs are under reconsideration. In a further development at the FDA,[13] the 5-year exclusivity awarded to new molecular entities has been extended to include category B FDCs: combinations containing an already authorized drug with a new investigational drug.

Concern 3: Justification Requirements for Category A and B FDCs

The FDA codevelopment guideline[8] clearly states a series of criteria that must be met before codevelopment of novel entities (category C) can be considered. However, in the case of category A and B combinations, the EMA clinical guideline[14] talks about balancing advantages and disadvantages but lacks clarity on priorities, in particular with regard to whether therapy simplification (convenience) can be the primary justification in certain cases or can come only secondary to the proof of an improvement of ''benefit/risk.'' The regulatory informants from the EU, however, agreed that from the EMA point of view, simplification of therapy (convenience) can never be the primary argument to justify the development of an FDC of already authorized drugs (category A). This appeared to be based on the perception that there is a lack of published evidence to support the relationship between convenience and compliance. However, the literature reveals that there are increasing numbers of papers that do support this relationship, not only for infectious disease (HIV and tuberculosis), but also for hypertension and other chronic diseases, such as diabetes, rheumatoid arthritis, and glaucoma. For review, see Bjerrum et al.[2] In addition, FDCs can be an important factor in compliance among the elderly, where polypharmacy is particularly common.[15] On this basis, there appears to be sizable evidence that the real-world effectiveness of FDCs can be substantially better than equivalent medication regimes using separate dosage units, even though the tested efficacy from clinical trials may be no different. The results of several of these compliance studies also point toward improved patient satisfaction and reduced health care costs from the use of FDCs.[16,17]

In the EU, consideration of the benefit/risk ratio is taken as the starting point for regulatory consideration of the justification for an FDC. However, there is an unclear relationship between ''benefit/risk'' and ''efficacy and safety,'' creating an additional source of confusion.[18] It is also recognized that

quantification of the benefit/risk relationship is difficult and that there is a need for the development of better benefit/risk models.[18,19] The amount of acceptable risk can depend on the therapeutic area, and assigning weight and value to different aspects of the benefit/risk relationship can be complex. The importance of this quantification can clearly be seen in the case of contrasting decisions being reached by the EMA and FDA on the basis of what are mainly subjective benefit/risk decisions by both agencies. For instance, the antidiabetes medication rosiglitazone and the associated FDCs Avandamet (rosiglitazone/metformin hydrochloride) and Avaglim (rosiglitazone/glimepiride) were withdrawn from authorization by the EMA in September 2010 on the basis of cardiovascular risk.[20,21] In the US, the equivalent medications continue to be marketed, as the cardiovascular risk was considered "concerning, but not definitive."[22] In a more recent case, the opposite situation occurred, when the Novo Nordisk basal insulin Tresiba (insulin degludec) and the associated FDC Ryzodeg (insulin degludec/insulin aspart) were approved by the EMA but rejected by the FDA on the basis of cardiovascular risk.[23] The need for quantification to make such decisions more comparable is part of the current drive at both the EMA and the FDA to make the regulation of medicines more science based and advance the role of regulatory sciences at the health authorities.[24,25]

Apart from benefit/risk, the concept of "clinical relevance" was raised by EU regulators as one of the basic justifications for any medicine to be authorized, including FDCs, although the word does not appear in the FDC guidelines. In fact, no official definition exists either in the EU guidelines or in the literature on the subject.[26] In clear contrast to the EU, the US informants did not see any need for justification of an FDC involving already authorized active ingredients—either from a benefit/risk perspective or from a clinical relevance perspective. Being already authorized, the ingredients were safe and effective, and market forces would determine if an FDC was justified.

Concern 4: A Need for Information on FDCs in More Disease Areas

The level of information on FDC development in disease-related guidelines from the EMA and the FDA varies significantly, even for diseases where FDCs are common or of interest (eg, HIV/AIDS, hypertension, diabetes). Although the EU informants regarded these guidelines as a suitable place to provide guidance on FDCs where such combinations are common practice, the dropping of information on FDCs from the latest draft of the EMA diabetes guideline[27] suggests a different approach at the EMA headquarters. In contrast, although the US informants did not see a need in this area, the FDA diabetes guideline[28] contains significant FDC information, demonstrating that there are differences of opinion at the FDA as well.

Concern 5: A Lack of Information Related to Biopharmaceuticals

The EMA clinical guideline on FDCs[14] refers directly to tablets and uses other words related to oral formulations. According to the industry informants, it is possible to follow the principles in the case of nonoral combinations, but it would be preferable if the guidelines were edited to more clearly include other formulations—in particular, intravenous delivery. The guideline would then be more relevant for biopharmaceuticals, which are becoming of increasing importance worldwide.

A clear response from both the EU and the US was that guidelines follow behind the demands of industry—there needs to be sufficient pressure from the number of questions emerging during scientific advice before a guideline will be developed or revised.

Further Comments

The FDA appears to have more interest than the EMA in promoting combinations of new investigational drugs, evidenced by the recent finalization of their codevelopment guideline.[8,29] This leads to a question raised during the industry interviews whether the presence or absence of guidelines is important for innovation. The increasing complexity of FDCs and medicines in general puts pressure on the role of guidelines. With new technologies—such as nanotechnology providing complex delivery mechanisms for chemotherapy FDCs,[30] armed antibodies with chemical toxins linked to the cancer-targeting antibody,[31] and devices that enable titration of one or more active ingredients (eg, Lixilan[32])—when is a combination an FDC? When do the guidelines apply? Scientific advice rather than guidelines becomes increasingly important. This may lead to the question, where does this leave guidelines?

Another main goal of the FDA codevelopment guideline[8] is to stimulate the collaborative development of combination drugs by different companies.[29] It is clearly important that potential FDCs are not limited by proprietary arguments of ownership of the individual components. Over recent years, with the pressure of the current economic, scientific, and drug development environment, pharmaceutical companies have been increasingly willing to form partnerships with one another and join public-private partnerships.[33–36]

This type of collaboration should clearly also extend to the regulatory authority level. Certain steps are being taken toward a globalized approach by the regulatory authorities.[37–39]

Parallel scientific advice involving the FDA and EMA is available but currently is little used. Increasingly frequent telephone conferences between the EMA and FDA on exchange of thoughts on various topics is helping to align scientific positions and increase mutual understanding. The prioritization of the role of regulatory science by both health authorities[24,25] provides a clear opportunity to harmonize such science-based approaches. The defining and harmonizing of terminologies will be another important step. However, as revealed during this project in relation to FDCs, in the ''real'' world, a number of basic approaches and attitudes need to be reviewed for global solutions to be possible.

Conclusion

It is clear from the results that the current regulatory environment for FDCs lacks consistency: in the terminology employed, between the nonclinical and clinical guidelines, between EMA and FDA perspectives on the clinical development of FDCs, in benefit/risk and justification decisions, and between disease areas. In addition, there appears to be a clear gap between the concerns of industry and those of the regulatory authorities. Such gaps and inconsistencies may create a barrier to innovation moving from the laboratory to the clinic, as companies cannot clearly see the development path requirements. It is therefore important that the health authorities work toward increasing clarity. Combination studies are likely to be seen as not only advantageous but necessary from the early stages of clinical development.[40] As expressed by the World Health Organization as long ago as 2005, ''the development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective,'' and ''it is important that access to useful, new FDCs should not be delayed by unnecessary constraints''.[41]

Although this project focused on FDCs, the topics raised highlight some of the major challenges that currently face the regulatory world. These challenges include how to improve the role of regulatory science and provide clear quantification in assessment decisions; the role of guidelines and their impact on innovation; and, perhaps most important, the question of globalization and how to move to a more harmonized regulatory system. The regulatory environment is clearly in a state of change as regulatory authorities in more regions define their regulatory structure (Brazil, Russia, India, China). Before these changes lead to even greater regulatory diversity around the world, it is imperative that a collaborating FDA and EMA take the opportunity now to move toward increasing harmonization. We live in a world of globally aware patients that demand new and effective treatments, with clearly identified efficacy and safety parameters, in the minimum time possible.

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References

1. Price Waterhouse Coopers. Pharma 2020: Virtual R&D, which path will you take? http://www.pwc.com/gx/en/pharma-life-sciences/pharma-2020/pharma2020-virtual-rd-which-path-will-you-take.jhtml. Published 2008. Accessed March 19, 2014.
2. Bjerrum OJ, Gautam Y, Honore PH, Vana V. Drug-drug combinations revisited. *Eur J Hosp Pharm*. 2014;21:8-12.
3. US Food and Drug Administration. Guidance for Industry: nonclinical safety evaluation of drug or biologic combinations. http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0004-gdl0002.pdf. Published 2006. Accessed March 18, 2014.
4. US Food and Drug Administration. Code of Federal Regulations Title 21, 21CFR3.2. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=3.2. Published 2013. Accessed March 19, 2014.
5. European Medicines Agency. Guideline on the non-clinical development of fixed combinations of medicinal products [EMEA/CHMP/SWP/258498/2005]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003976.pdf. Published 2008. Accessed March 19, 2014.
6. Marshall MN. The key informant technique. *Fam Pract*. 1996;13:92-97.
7. Boyce C, Neale P. Pathfinder international tool series: monitoring and evaluation—2. Conducting in-depth interviews: a guide for designing and conducting in-depth interviews for evaluation input. http://www.cpc.unc.edu/measure/training/materials/data-quality-portuguese/m_e_tool_series_indepth_interviews.pdf. Published 2006. Accessed March 19, 2014.
8. US Food and Drug Administration. Guidance for industry: codevelopment of two or more new investigational drugs for use in combination. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf. Published 2013. Accessed March 19, 2014.
9. Hughes B. Novel agents combined get own guidance. *Nat Biotechnol*. 2011;29:174.
10. Kahrstrom CT. In the news: new TB drug cocktail. *Nat Rev Microbiol*. 2012;10.
11. National Research Council. Facilitating collaborations to develop combination investigational cancer therapies: workshop summary. http://www.nap.edu/catalog.php?record_id=13262. Published 2012. Accessed March 19, 2014.
12. European Medicines Agency. Concept paper on the need to revise the guideline on the clinical development of fixed dose combinations of medicinal products regarding dossier content

requirements [EMA/CHMP/779887/2012]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139482.pdf. Published 2013. Accessed March 19, 2014.
13. US Food and Drug Administration. Guidance for Industry: new chemical entity exclusivity determinations for certain fixed-combination drug products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf. Published 2014. Accessed March 19, 2014.
14. European Medicines Agency. Guideline on clinical development of fixed combination medicinal products [CHMP/EWP/240/95]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf. Published 2009. Accessed March 19, 2014.
15. Dickson M, Plauschinat CA. Compliance with antihypertensive therapy in the elderly: a comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. *Am J Cardiovasc Drugs*. 2008;8:45-50.
16. Hutchins V, Zhang B, Fleurence RL, Krishnarajah G, Graham J. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. *Curr Med Res Opin*. 2011;27:1157-1168.
17. Bell DS. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. *Diabetes Obes Metab*. 2013;15:291-300.
18. Liberti L, McAuslane N, Walker SR. Progress on the development of a benefit/risk framework for evaluating medicines. http://cirsci.org/system/files/private/2010FocusLiberti_0.pdf. Published 2010. Accessed March 19, 2014.
19. European Medicines Agency. Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use [EMEA/CHMP/15404/2007]. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf. Published 2008. Accessed March 19, 2014.
20. European Medicines Agency. Press release: European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim [EMA/585784/2010]. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf. Published 2010. Accessed March 19, 2014.
21. Pouwelsa KB, Grootheesta KV. The rosiglitazone decision process at FDA and EMA. What should we learn? *Int J Risk Saf Med*. 2012;24:73-80.
22. Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the US Food and Drug Administration. *N Engl J Med*. 2010;363:1489-1491.
23. PMLiVE. FDA turns down Novo Nordisk's Tresiba and Ryzodeg. http://www.pmlive.com/pharma_news/fda_turns_down_novo_nordisks_tresiba_and_ryzodeg_463186. Published 2013. Accessed March 18, 2014.
24. European Medicines Agency. European Medicines Agency process for engaging in external regulatory sciences and process improvement research activities for public and animal health [EMA/14946/2013]. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139888.pdf. Published 2013. Accessed March 19, 2013.
25. US Food and Drug Administration. Advancing regulatory science at FDA, a strategic plan. http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm. Published 2011. Accessed March 19, 2014.
26. Putzeist M, Mantel-Teeuwisse AK, Aronsson B, et al. Factors influencing non-approval of new drugs in Europe. *Nat Rev Drug Discov*. 2012;11:903-904.
27. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus [CPMP/EWP/1080/00]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Published 2012. Accessed March 19, 2014.
28. US Food and Drug Administration. Guidance for Industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. http://www.fda.gov/downloads/Drugs/Guidances/ucm071624.pdf. Published 2008. Accessed March 19, 2014.
29. Woodcock J, Griffin JP, Behrman RE. Development of novel combination therapies. *N Engl J Med*. 2011;364:985-987.
30. Ramsay EC, Dos SN, Dragowska WH, Laskin JJ, Bally MB. The formulation of lipid-based nanotechnologies for the delivery of fixed dose anticancer drug combinations. *Curr Drug Deliv*. 2005;2:341-351.
31. Pollack A. Drug Information Agency daily news. FDA approves a new drug for advanced breast cancer, 22 Feb 2013. http://www.diahome.org/en-GB/News-and-Publications.aspx. Published 2013. Accessed March 19, 2014.
32. Zealand Pharma. Pipeline. http://www.zealandpharma.com/product-pipeline. Published 2014. Accessed March 19, 2014.
33. Bjerrum OJ, Linden HH. European new safe and innovative medicines initiatives: history and progress (through December 2009). In: Littman BH, Krishna R, eds. *Translational Medicine and Drug Discovery*. Cambridge, England: Cambridge University Press; 2011;265-288.
34. Critical Path Institute. Critical path to TB drug regimens. http://c-path.org/programs/cptr/. Published 2014. Accessed March 19, 2014.
35. Goldman M. The innovative medicines initiative: a European response to the innovation challenge. *Clin Pharmacol Ther*. 2012;91:418-425.
36. US Food and Drug Administration. Critical Path Initiative. http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm. Published 2013. Accessed March 19, 2014.
37. European Medicines Agency. Road map to 2015: the European Medicines Agency's contribution to science, medicines and health. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf. Published 2010. Accessed March 19, 2014.
38. International Conference on Harmonisation. The value and benefits of ICH to drug regulatory authorities—advancing harmonization for better health. http://www.ich.org/fileadmin/Public_Web_Site/News_room/C_Publications/ICH_20_anniversary_Value_Benefits_of_ICH_for_Regulators.pdf. Published 2010. Accessed March 19, 2014.

39. US Food and Drug Administration. Global engagement. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM298578.pdf. Published 2012. Accessed March 19, 2014.
40. Pourkavoos N. Unique risks, benefits, and challenges of developing drug-drug combination products in a pharmaceutical industrial setting. *Combination Products in Therapy*. 2012;2:1-31.
41. World Health Organization. Annex 5, guidelines for registration of fixed-dose combination medicinal products [WHO Technical Report 929]. http://apps.who.int/medicinedocs/documents/s19979en/s19979en.pdf. Published 2005. Accessed May 27, 2014.
42. International Conference on Harmonisation. ICH harmonised tripartite guideline: non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, M3 (R2). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf. Published 2009. Accessed March 19, 2014.