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EU Medical Device Approval Safety Assessment

A comparative analysis of medical device recalls 2005-2009

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Executive Summary

- The process for the review and approval of new medical devices in the US is currently under tremendous scrutiny. In the face of questions about the consistency and variability of the device approval process many have questioned whether the current 510(k) clearance and PMA processes are adequately ensuring the approval of safe and effective medical devices, or if more stringent review processes are needed.

- As device approvals have become increasingly challenging in the US there has been a shift towards companies obtaining approval of their most innovative technologies in Europe first, often years before the same technologies are approved in the US.

- Faced with a situation in which patients in the US are denied access to technologies available in Europe a central question is whether the approach adopted in the US is protecting patients in America from unsafe medical devices, or if the rate of serious product recalls in Europe and the US is in fact the same.

- By analyzing publically available data on severe recalls in Europe (equivalent to a Class I recall in the US) this study shows that the number of recalls in Europe is identical to that in the United States, and the therapeutic mix and type of recall is also similar to that in the US.

- This initial assessment of comparable recalls between the US and Europe does not suggest that different approval processes, and earlier approvals, in Europe come at a cost in terms of patient safety.

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I. Introduction

This is a period of tremendous flux and uncertainty in the medical device industry. Changes to the current medical device approval process are being considered by regulators in both the US and EU. The FDA is currently reviewing the US 510(k) process to improve the approval & monitoring of medical devices in the US, while the European Commission (EC) is also exploring changes to the Medical Device Directive (MDD) and IVD Directive (IVDD) to increase potential robustness of the EU process.

There are many differences between the approach taken to reviewing and approving new medical devices in Europe and the US. The centralized approach to medical device approvals the FDA has taken is fundamentally different than the decentralized model the EC has implemented with a significant impact on the approval process, requirements, and timing. As a consequence of differences in approach many observers have pointed to the outcome that new medical devices, and in particular the most novel devices, such as those approved under the Pre Marketing Approval (PMA) process in the US, are almost always approved in Europe well before the US. An open, and so far unanswered, question is whether this earlier approval in Europe has been at the expense of patient safety? More specifically is the rate of recalls of medical devices in Europe different from that in the US as a consequence of their earlier adoption of "unproven" medical technologies?

The current EU system is governed by three EC directives: the Medical Device Directive, the In-Vitro Diagnostic Directive, and the Active Implantable Medical Device Directive. Guidelines for approval are laid out in these EC directives, but the actual approval systems are coordinated at the country level. Each country's Competent Authority (CAs) certifies for-profit "Notified Bodies" (NBs), standards organizations that are authorized to approve a variety of goods for the EU market and grant a CE mark certification. These NBs often cover a wide range of goods, from industrial to medical products. Among the current Notified Bodies, there are 74 separate entities across 25 countries with the authorization to approve medical devices for the EU market. A manufacturer seeking to market a new medical device in the EU must select one of these 74 Notified Bodies to certify the new device applications with the CE mark. Based upon the device classification the NB will request certain materials (e.g. a literature review or clinical data) and perform manufacturing quality assessments on the manufacturing process. Upon satisfactory review and approval, a CE mark is awarded, enabling access to the entire EU market.

Recent high-profile device recalls have increased focus on the US device approval process, with some advocating for a more stringent review of new devices. However, among companies there is a growing concern that such changes to the approval process and timelines may do little to improve patient safety. or more specifically if there is even a safety problem with the system as is at all. Several recent studies on the rate of device recalls in the US have reached similar conclusions. A study by Ralph Hall at the University of Minnesota estimated a rate of recall of 0.45% for 510(k)-approved devices, based on the annual average number of 510(k) submissions over the past 10 years. A similar study by the Battelle Memorial Institute estimated a rate of recall of 0.16% based on the total number of 510(k) approvals since 1998. Both studies obtained recall data from FDA's Medical and Radiation Emitting Device Recall database and focused exclusively on the United States.

II. Study Methodology

A primary challenge of a comparison between the US and EU system is one of terminology. The EU system does not report device "recalls," but rather Field Safety Corrective Actions (FSCAs). While a FSCA may be a recall, it can be another action, such as a device modification or simply increased surveillance by patients or providers who use the device.

Another major challenge limiting a comparison between the EU and US is the lack of a centralized authority for medical device approvals and tracking in the EU. Given the absence of a central governing body, there is no comparable public database that captures all medical device safety recalls in the EU as FDA does in the US. Additionally, because approval occurs between two private organizations (the manufacturer and the Notified Body that CE marks the product), there is no publicly available approval data. Thus, a comparison of absolute recall rates is not feasible as the number of approval submissions or on-market devices cannot be publically determined.

This study took a four phase approach to building a database of FSCAs to enable a suitable comparison to US recalls as outlined in Exhibit I. Phase 1 consisted of reviews of EU guidance documents, interviews with CA officials and publically available data. Although there is no centralized body in the EU that publishes approval or recall data, several of the most active EU member states do publicly post medical device field safety notices (FSNs) on their websites. All member countries also report major safety issues to the European Commission through National Competent Authority Reports (NCARs) when a safety issue is reported by a company that is based, or has an Authorized Representative, in the country. Thus, a key assumption in the methodology is that NCARs and MDAs (UK safety alerts) represent all serious safety events in the EU, based on conversations with officials at EU Competent Authorities.

In Phase 2, a comprehensive dataset was created from public FSNs and NCARs to facilitate a comparison to the US. The EC website lists 1,412 NCARs from 2005-2009 across 24 countries. While all EU competent authorities file NCARs, the majority of medical device reporting activity is concentrated in 5 countries, representing 85% of all NCARs from 2005-2009: the UK, Germany, Switzerland, Ireland, and France. These countries have well-developed medical device industries with active oversight bodies that post large numbers of safety notices publicly. Additionally, combined they list 5,034 medical device related field safety notices from 2005-2009.

All available notices in the above 5 countries (5,034 notices) were standardized and manually coded by therapeutic area and company to provide a comprehensive data set in Phase 3. These Field Safety Notices were then matched to the EC's NCAR list based on the local reference number captured in the NCAR inventory for all 5 countries except the UK and France. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) reviews manufacturer Field Safety Notices and publishes Medical Device Alerts (MDAs) which provide guidance to the public. Although MDAs cannot be linked directly to the NCAR database, they provide a similarly complete picture of safety issues in the UK and were used in this analysis. Records from the French database could not be linked to the NCAR database due to lack of reference numbers, and these were not examined in this analysis. Overall, 849 of the 1,412 unique FSNs were identified and matched between CAs and the EC NCAR database.

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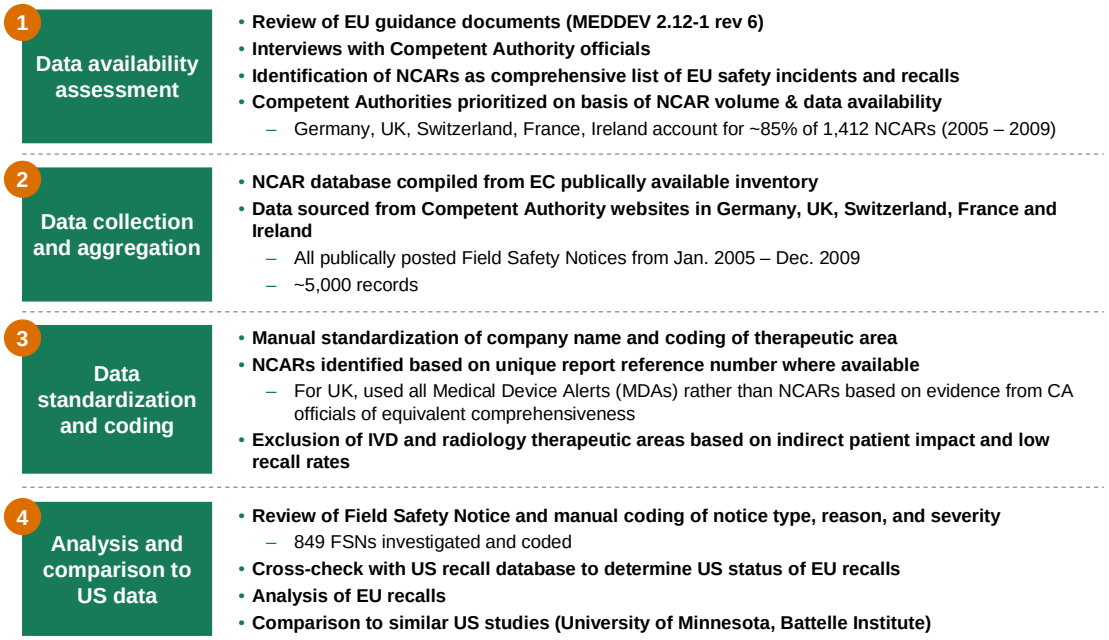
Exhibit I: Study methodology



In Phase 4, these records were prioritized by severity of recalls: 216 IVD and radiology records were excluded due to the low rate of severe recalls of these product types and their indirect impact on patient health. The corresponding company safety notices of the remaining 633 FSNs were then individually reviewed and coded for safety notice type, reason for recall, and severity of recall. Because the EU system does not assign a recall class, severity was determined according to the US system based on FDA guidelines. (See Exhibit II)

- Low (Class III) - Little chance that using or being exposed to the device will cause health problems
- Moderate (Class II) - Possibility that the device will cause temporary or reversible health problems or remote chance that the device will cause serious health problems
- Severe (Class I) - Reasonable chance that the product will cause serious health problems or death

These severe and moderate recalls were independently coded by two reviewers. In this case of disagreement, the notices were reviewed together and additional research performed to determine the appropriate classification. This was especially useful in some cases of assigning reasons for recall, as noted below. Duplicate records were removed and the remaining moderate and severe recalls were cross-checked against FDA's Medical and Radiation Emitting Device recall database. Any recall which was found to have occurred in the US was assigned its FDA classification. This final set of Class I-comparable recalls was analyzed across various dimensions and scaled up according to the ratio of NCARs examined to total NCARs (1.66x) to provide an approximation of the total number of recalls in the EU from 2005-2009.

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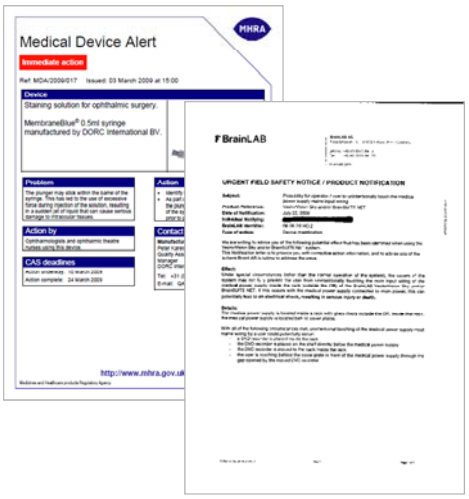
Exhibit II: FSN classification definitions

FSNs individually reviewed and mapped to FDA recall classification based on associated risk level



Individual Field Safety Notices read and classified	FDA Classification	BCG-assigned risk level
	Class I • Reasonable chance that the product will cause serious health problems or death	**Severe** • Death • Major injury • Severe infection • Major revision surgery
	Class II • Possibility that the device will cause temporary or reversible health problems • Remote chance that the device will cause serious health problems	**Moderate** • Extended surgery time • Significant blood loss • Life supporting device with backup available • Minor infection • Incorrect display with no effect on treatment
	Class III • Little chance that using or being exposed to the device will cause health problems	**Low** • Delay of non-critical patient treatment • External leak • Obvious mislabeling

Source: BCG Analysis

III. EU severe recall analysis and findings

Of the 849 Field Safety Notices examined, 102 were initially classified as severe recalls. Of these, 17 were excluded as they were not product recalls or corrective actions (e.g. reminders for proper use or medical updates regarding an entire category of products). Finally, a cross-check with the FDA's recall database found the initial classifications to be conservative. Of the 102 initially classified as severe, 27 were found to be Class II recalls in the US, while of the 339 initially classified as moderate, only 5 were found to be US Class I recalls**.**

In order to correct for the sample size of FSNs chosen for the study, a scale factor was then employed to extrapolate to the full number of EU recalls from 2005-2009. The 849 FSN examined represents 60.1% of the 1,412 total NCARs recorded by the European Commission. By applying a 1.66 scale factor the total number of Class I-comparable recalls in the EU (excluding IVD and radiology) is estimated to be 105, or 21 per year from 2005-2009. (See Exhibit III).

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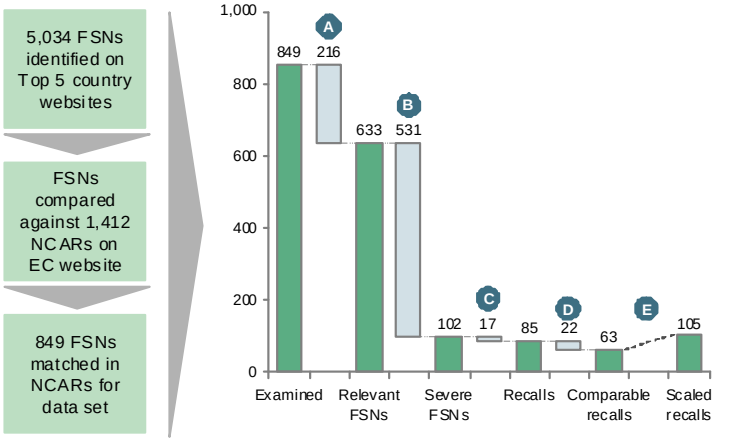
Exhibit III: 63 "Class I-comparable" FSNs identified

Data set consisted of 849 FSNs

Various filters applied to data set to ensure comparability to US studies



Filter applied

- **A** IVD and diagnostics excluded
  - 216 FSNs excluded from analysis due to low rate of severe recalls
- **B** Lower risk FSNs excluded
  - 531 Class II, III, duplicate recalls
- **C** Non-recalls excluded
  - Eliminate information updates, guidance, others
- **D** US FDA database check
  - Ensure classification is aligned and not too conservative
- **E** Scale-up factor of 1.66 applied[1]

Scale up factor of ~1. 66x based on ratio of NCARs / MDAs examined

1. Scale-up factor based on 1,412 total NCARs / 849 examined NCARs for 2005-2009
Source: BCG EU recall database, BCG analysis

Recalls are most concentrated in Cardiovascular and General Hospital therapeutic areas, representing 35% and 32% of all recalls respectively. Cardiovascular includes devices such as pacemakers, ICDs, AEDs, and vascular balloons, while General Hospital includes devices such as infusion pumps and sets, catheters, and needles. (See Exhibit IV.)

Most recalls were due to either manufacturing (~34.8%) or design issues (~27.3%). In some cases, it is difficult to distinguish between design and manufacturing issues based on the publically available data. For example, a catheter tip may detach due to a design flaw in which it was not specified correctly or a manufacturing flaw. Similarly, manufacturing issues and supplier issues are also often difficult to distinguish. Reasons for recall also vary across therapeutic area. Cardiovascular recalls are almost exclusively design or manufacturing issues, while other therapeutic areas have more diverse reasons for recall. The relatively high percentage of labeling errors in Orthopedics is mostly due to size labeling.

Reasons for recall can fall within two different categories: “pre-market” – issues that should be discovered in the approval process, or “post-market” – issues that could not have been prevented by a more stringent approval process. The EU rate was found to be 46% for pre-market issues and 54% for post-market issues.

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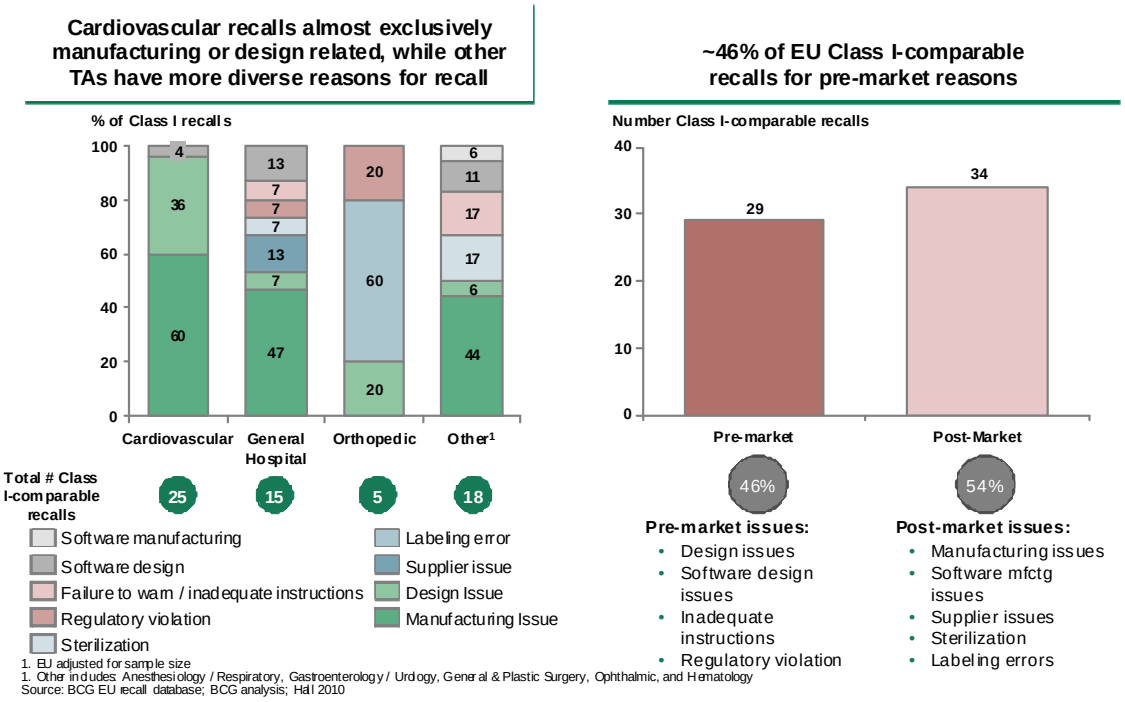
Exhibit IV: Reason for recall varies by therapeutic area

46% EU recalls due to pre-market issues



1. EU adjusted for sample size
1. Other includes Anesthesiology / Respiratory, Gastroenterology / Urology, General & Plastic Surgery, Ophthalmic, and Hematology

Source: BCG EU recall database; BCG analysis; Hall 2010

V. Comparison of EU recall findings to recent US studies

Of the notices initially classified as moderate or severe, 126 (28.2%) could be matched to recalls in the FDA Medical and Radiation Emitting Device recall database, resulting in the identification of 23 Class I and 103 Class II recalls. Date information was also available for both the EU and US notices (see Exhibit V.) The Class I recalls were evenly split, with 12 posted in the US first and 11 posted in the EU first. For Class II recalls, however, 61% were posted in the EU first and 39% were posted in the US first. This is likely due to the different regulatory stances taken by the bodies: in the US, the FDA creates its own recall report after discussing the recall with the manufacturer, while in the EU, most competent authorities simply post the manufacturer's safety notice without creating a report for the public. The exception is the UK, which summarizes the safety notice in a Medical Device Alert.

In the US, Hall found that 55% of recalls relate to post-market issues, while 45% relate to pre-market issues. The EU rate was found to be nearly identical at 54% for post-market issues and 46% for pre-market issues, reinforcing the findings that systems perform similarly well for pre-market approval.

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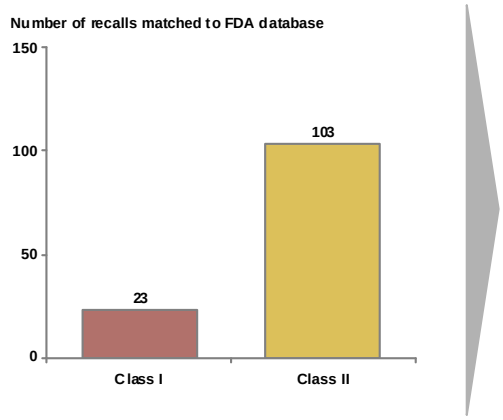
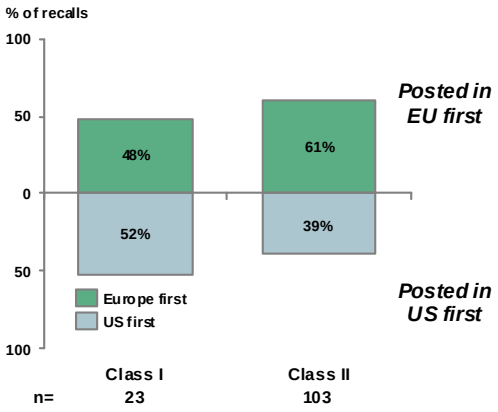
Exhibit V: 126 EU notices matched to the US FDA database

Many EU notices posted earlier than in the US

EU notices matched to US FDA recall database across classes[1]...



...with the EU posting more Class II recall notices earlier than the US



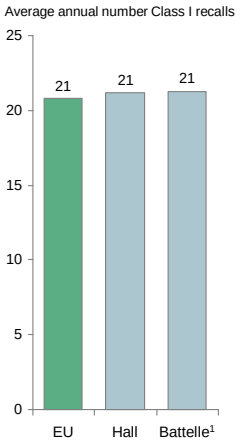
On average, EU notifications posted ~3 weeks earlier than the US

1. Includes BCG-classified "Moderate" recalls. Note: Some recalls unable to be matched due to local lot recalls or different trade names
Source: BCG EU recall database, FDA

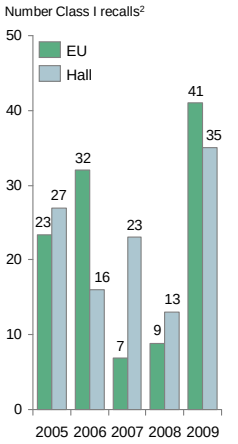
Exhibit VI: Recalls similar in EU and US across dimensions

Comparison across absolute number, frequency and type

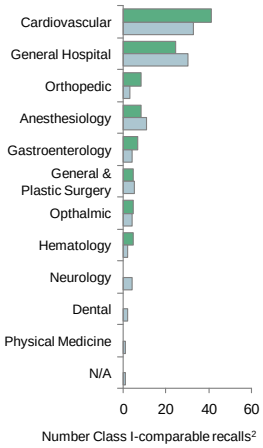
Estimates of annual Class I recalls in EU and US nearly identical



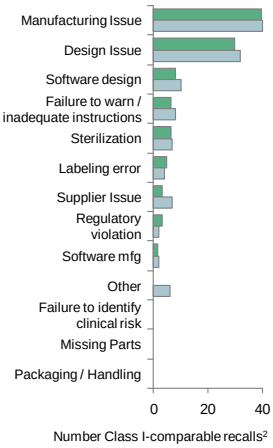
Pronounced increase in recalls in 2009 for EU and US



Class I-comparable recalls by therapeutic area[2]



Class I-comparable recalls by reason[2]



1. Includes IVD and radiology 2. Scaled for EU recall sample size (1.66x)
Source: BCG EU recall database; BCG Analysis; Hall 2010; Battelle 2010

Overall the absolute number of annual recalls from 2005-2009 is similar between the EU and the US, ~21 (See Exhibit VI). The distributions across therapeutic areas and the reasons for recall are also nearly identical as well, with most of the recalls occurring in the Cardiovascular and General Hospital spaces and relating to manufacturing or design issues. Recalls may be concentrated in the Cardiovascular and General Hospital spaces due to the high volume and critical nature of the devices included in the category, such that a small defect could result in a significant health issue.

Although the University of Minnesota study and the Battelle study both focused exclusively on recalls in the US and retrieved data from FDA's online database, there were differences between the two studies as well. Hall reported 118 unique Class I recalls from 2005-2009, of which 12 were in-vitro diagnostics or radiology. The Battelle study reported approximately 116 unique Class I recalls from 2005-May 2010, but did not analyze the recalls by therapeutic area. Exhibit VII contains a summary comparison of the EU study with the University of Minnesota study and the Battelle study.

Exhibit VII: Comparison with previous US studies suggest EU safety system as effective as US system

	EU Safety study	Prof. Ralph Hall	Battelle Study
Study Focus	EU NCARs / UK MDAs	Class I recalls	510k recalls
Period captured	2005-2009	2005-2009	Jan. 2005-May 2010
Estimated Class I Recalls	21 per year	21.2 per year	21.6 per year (inc IVD & radiology)
Public Availability	~60% of NCARs & MDAs	100% of US records	100% of US records
Initial database	~5,000 records	474 records	Unknown
Publically available data fields	• Company • Product • Safety notice date • (Safety notice type)	• Company • Product • Recall date • Recall severity • Approval pathway	• Company • Product • Recall date • Recall severity • Approval pathway
Manually coded data fields	• Therapeutic area • Reason for recall • Safety notice type • Severity of Recall	• Therapeutic area • Reason for recall • Product code • Third-party review	• Reason for recall • Corrective action

EU system with roughly the same number of Severe Class I recalls as US

Factoring in device lag, likely that overall recall rates virtually identical to US

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VI. Conclusion & further research

The results of this study suggest little difference between absolute number of serious recalls between the US and EU regulatory systems. The distribution of the serious recalls is similar across therapeutic areas and reasons for recall, suggesting that differences between the two systems do not ultimately affect performance. In addition, given the expectation that the EU approves more devices than the US it is likely that the EU recall rate may actually be slightly lower than the US rate.

The robustness of these findings could be further improved with additional research and greater participation of industry and regulatory players. Although the ultimate outcome (number and kind of serious recalls) of the EU and the US regulatory systems is similar, more detailed research into specific product recalls would help inform whether there are best practices that could be instituted. Additionally, the overlap between devices that are approved in either or both the EU and the US would shed further light on the timelines and relative strengths and weakness of each system. If many more devices are approved in the EU than the US, or vice-versa, the recall rate could be lower despite similar absolute recall rates.

VII. Appendix

Definitions

Competent Authority: EU country government organizations that oversee regulatory compliance and market vigilance

Notified Body: Private organizations certified by Competent Authorities to grant CE-mark status to products that meet regulatory standards

Field Safety Notice: Notice sent by manufacturer informing customers and relevant parties of a safety issue or recall

Field Safety Corrective Action: Manufacturer recommendation for action in the event of a safety incident in the EU; similar to, but not exactly the same as, US recal

NCAR: National Competent Authority Report sent to the European Commission and member countries in the event of a serious adverse event. Not publicly available.

Medical Device Alert: Report issued by the MHRA in the UK giving guidance on manufacturer field safety notices

Key assumptions

1. NCARs and MDAs represent all serious safety events in the EU
    - Based on conversations with officials at EU Competent Authorities

2. Recall distribution across therapeutic areas and reason for recall is equivalent across all EU countries
    - EU countries with most NCARs and public records selected for analysis

Sources

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