Journal of Diabetes Science and Technology
Volume 7, Issue 2, March 2013

COMMENTARY

Considerations for an Institution for Evaluation of Diabetes Technology Devices to Improve Their Quality in the European Union

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Abstract

All medical devices used for self-monitoring of blood glucose (BG), insulin injection, continuous subcutaneous insulin infusion, and continuous glucose monitoring in the European Union (EU) must have a Communauté Européenne (CE) mark. However, the approval process for obtaining this mark is different from that used by the European Medicines Agency in the EU for drugs or by the Food and Drug Administration in the United States for such medical and *in vitro* diagnostic devices. The notified bodies involved in the CE mark process perform this evaluation in cooperation with the manufacturers. They have only limited diabetes know-how; they have to handle all kinds of medical devices. There are devices for therapy on the market in the EU (i.e., they have market approval) that do not fulfill quality requirements, as indicated, for example, in the international norm ISO 15197 for BG test systems. Evaluation of the performance of such systems is usually provided by the manufacturers. What is missing in the EU is an independent institution that performs regular and critical evaluation of the quality of devices used for diabetes therapy before and also after their market approval. The work of such an institution would focus on BG test systems (these represent two-thirds of the market of medical devices for diabetes treatment) but would also evaluate the performance of other devices. It has to be clarified what legal framework is required for such an institution and how it can be financed; probably this can be done in a shared manner by the manufacturers of such devices and the health insurance companies. Positive evaluation results should be a prerequisite prior to any reimbursement for such devices.

J Diabetes Sci Technol 2013;7(2):542–547

Introduction

Since the 1980s, we have seen a tremendous upswing in the use of medical devices for diagnostics and therapeutic measures in diabetes therapy. Today diabetes technology (DT) represents a cornerstone of modern diabetes therapy. We have come a long way from the first test strips to modern blood glucose (BG) test systems, from insulin pumps the size of a backpack to patch pumps. The availability of artificial pancreas systems for practical use was also never closer than today, as the first clinical trials under home use conditions have already been performed. The development

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Abbreviations: (BG) blood glucose, (CE) Communauté Européenne, (DDTD) diabetes diagnostic and therapy devices, (DT) diabetes technology, (EU) European Union, (FDA) Food and Drug Administration, (ISO) International Organization for Standardization, (SKUP) Skandinavisk Utprøving av Laboratorieutstyr for PrimæRhelsetjenesten, (SMBG) self-monitoring of blood glucose

Keywords: analytical performance, blood glucose, blood glucose meters, insulin pens, insulin pumps, point-of-care testing, quality evaluation

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of smartphones also brings such computer power to any user that software applications for patients with diabetes have started to become very popular.

In contrast to these rapid technological developments, the regulatory handling of medical devices has made relatively slow progress. In Europe, the Communauté Européenne (CE) mark process within the European Union (EU) was implemented in 1993 by bringing the Medical Device Directive into force (*eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML*). Some years later, the *In Vitro* Diagnostic Directive provided the legal framework for market approval of new devices, including those used for diabetes therapy (*eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:331:0001:0037:EN:PDF*). In this article, all medical devices or *in vitro* diagnostic devices will be referred to as "diabetes diagnostic and therapy devices" (DDTD). Nevertheless, the approval process for obtaining a CE mark for DDTD is different from that used by the European Medicines Agency in the EU for drugs or by the U.S. Food and Drug Administration (FDA) for medical devices. Notified bodies play an important part in the CE marking process; there exist a considerable number (>70) of such institutions for medical devices across Europe (*ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=search.notifiedbody*). They evaluate the quality of the documentation provided and can ask for additional data, but it appears as if a number of these have no in-depth knowledge of DDTD as they have to handle different kinds of medical devices. In short, getting market approval for DDTD in the EU apears to be easier than in the United States where the FDA asks for much more documentation and study data, especially for new types of DDTD. Morevoer, after market approval of such a device, there is no regulatory requirement—neither in the EU nor in the United States—to conduct independent evaluations of, e.g., the measurement quality of new batches of test strips for BG test systems in random samples. This is done only by the manufacturers themselves.

The CE mark system has been heavily criticized in light of the scandal of silicone breast implants in France. Subsequently, a number of measures were proposed to increase the quality of this approval process in the EU; however, in view of the complexity of the EU situation, this is a political process that most probably will take some time before changes are implemented.

The aim of this commentary is to stimulate an initiative for establishing an independent institution in Europe that evaluates the quality of DDTD.[1] Positive evaluation of any new DDTD or any of its essential parts by the proposed institution should be an essential prerequisite prior to their reimbursement. First, such an institution must establish standards for evaluating DDTD; this should be done by experts in DT in close communication with academic and industry partners.

Are Diabetes Diagnostic and Therapy Devices Less Risky in Comparison with Antidiabetic Drugs?

One might say that DDTD are not life threatening, as they cannot induce, e.g., a hypoglycemic event *per se* like an antidiabetic drug can, i.e., they are not as dangerous as insulin. However, if, e.g., BG test systems measure too high values in comparison with the real BG values [70 mg/dl instead of 55 mg/dl, which is still acceptable according to the International Organization for Standardization (ISO) norm (±15 mg/dl], this could induce an immediate risk for the patients by delaying recognition of hypoglycemia and the related appropriate action or by selecting inappropriately high insulin doses [BG of 240 mg/dl instead of 200 mg/dl (±20%)] that might subsequently lead to hypoglycemic events. Also, BG systems that systematically measure too low glucose values may please the patients and their treating physician when reviewing their glucose profiles, but the consequence is chronically elevated BG levels that are associated with an increased risk of developing diabetes-related complications. Likewise, systematically too high values can increase the risk of hypoglycemia. Thus, inappropriate measurement quality of BG systems is highly relevant because the outcome can be potentially severe or at least increase the morbidity of patients with diabetes.

Process of Communauté Européenne Marking

The CE mark is a prerequisite for all devices, including medical devices that are distributed in the EU, and it confirms the compliance with essential requirements prescribed in directives for the respective product category

(ec.europa.eu/enterprise/policies/single-market-goods/cemarking/). With the application of the CE mark on a medical device, the manufacturer declares that the product meets the EU requirements and that the required conformity evaluation procedures were performed in cooperation with a notified body.

Concerning system accuracy of BG test systems, the internationally accepted standard DIN ISO 15197:2003 defines performance requirements. For application of the CE mark on a BG test system, these requirements should be fulfilled. However, clinical–experimental evaluations indicate that a considerable number of DDTD available on the market, in fact, do not meet the requirements.[2,3] It is obvious that the currently employed CE mark process does allow "black sheep" to bring their potentially dangerous DDTD or, e.g., batches of test strips to the market. Unfortunately, the (current) CE mark system lacks transparency, i.e., it is not publicly known how many DDTD are passing through the CE process each and every year and what information was provided by the manufacturers to get the CE mark. While the FDA has the Freedom of Information Act, a law that requires granting public access to the documents used for the medical approval process—the EU does not.

Range of Diabetes Diagnostic and Therapy Devices Used for Diabetes Diagnosis/Therapy

It is of note to see the range of applications in which DDTD are used: continuous glucose monitoring, insulin pens, insulin pumps, and more. This list of DDTD, albeit incomplete, underscores the complexity and diversity of the world of DT nowadays and necessitates the involvement of experts for each indication to evaluate if a given device fulfills the necessary quality requirements before market approval is given. Thus, the proposed institution should also support the notified bodies during the CE mark process by providing expert opinions.

Blood glucose test systems are not only used for self-monitoring of blood glucose (SMBG) by people with diabetes, they are much more widely used nowadays: in intensive care units, in emergency situations, in outpatient clinics. The requirements for the measurement quality of BG test systems used by medical personnel are clearly different from that for SMBG.

Evaluation of the Performance Quality of Blood Glucose Test Systems for Approval

For the users (and the prescribing physicians), it is virtually impossible to keep abreast of the plethora of BG systems that are on the market and/or newly released each and every year (which also reflects that this is a good business). In addition to the established companies that have lengthy experience in developing BG systems, there are an increasing number of new companies bringing such systems to the market. Most companies never publish/present the data used for market approval (i.e., the data needed for the CE mark process). Most often, such evaluations are performed against a laboratory glucose analyzer rather than against a true reference method that allows traceability of the measurement results, and there are no head-to-head comparisons with other BG systems. In the past, some manufacturers have financed the performance of such studies.[2–4] The published results present a very different picture of a wide range of measurement quality for tested BG systems [device with tested strip lot(s)]. The performance ranges from excellent (BG system will also fulfill the new requirements of the draft EN ISO DIS 15197:2011, i.e., system has a measurement error <15 mg/dl below 100 mg/dl and <15% above) to average (accuracy is within the requirements of the present standard EN ISO 15197:2003, <15 mg/dl below 75 mg/dl and <20% above) to a considerable number of systems with poor measurement quality (accuracy does not meet the requirements of the present ISO standard).

Inappropriate Reimbursement Policies and Missing Reaction of Authorities after Approval

In some countries, it appears as if the measurement quality is completely ignored because the reimbursement policies focus primarily on the price of the BG test systems. This approach is questionable as it imposes a relevant medical risk on the patients with diabetes. In addition, it also appears as if the authorities/regulating bodies in the EU do not react appropriately with respect to the black sheep mentioned earlier: ~20% of the BG test systems on the market do not

comply with the current ISO standard. Applying the higher quality requirements of the anticipated revision of EN ISO 15197:2013 would lead to the situation where ~50% of BG test systems have an unacceptable measurement quality. We clearly believe that this ignorance and political neglect cannot be accepted and that establishing the proposed institution would be an appropriate action. It is disturbing that there is no established process for immediate action to remove DDTD that do not fulfill the official quality requirements (or at least an unacceptable batch of test strips) from the market. The expectation of the regulatory bodies that the market participants will solve the regulatory problems by themselves in a reasonable way has not materialized.

Evaluation of the Performance Quality of Blood Glucose Test Systems after Approval

After a given BG test system has gained market approval from the EU, there are no independent institutions who check the measurement quality of this system ever again (to our knowledge, this is also the case in the United States). Clearly, a key issue is the quality of test strip batches; this is evaluated only by the manufactures themselves. Insiders know how important it is to choose a "good" batch of test strips so that a BG test system can pass a test (e.g., for approval) and that there are considerable batch-to-batch differences in measurement quality.[5] This variability between batches of test strips can even exceed the acceptance limits of the present ISO norm.[6,7]

We believe that it is mandatory that an independent professional institution sytematically evaluate the measurement quality of BG test systems under daily life conditions with random samples, even years after approval, because this task cannot be delegated to the people with diabetes. It seems that there is no political awareness that BG systems require ongoing quality control during their complete lifetime by an independent institution, within a legal framework, to provide reliable and fast results.

An Example of an Independent Institution for Evaluating Diabetes Diagnostic and Therapy Devices: Skandinavisk Utprøving av Laboratorieutstyr for PrimæRhelsetjenesten

Although there is currently no independent institution active on an EU-wide level to ensure sufficient quality of DDTD on the European market, there is at least one institution that already performs such evaluations in an independent and standardized manner: the Skandinavisk Utprøving av Laboratorieutstyr for PrimæRhelsetjenesten (SKUP; Scandinavian evaluation of laboratory equipment for primary healthcare). The SKUP was established in 1997 at the initiative of professionals and health authorities and represents a cooperation between Norway (NOLKUS), Sweden (Equalis), and Denmark (Department of Clinical Chemistry, Odense University Hospital). The SKUP is led by a Scandinavian expert group; the secretariat is located in Bergen, Norway.

The legal provisions established in these three countries enable them to regulate the access of DDTD to their markets. In Norway, a requirement for test strip reimbursement is the standardized evaluation of the SMBG system. This is probably the main reason why only 14 different SMBG systems are on the Norwegian market.[8]

The SKUP supports the idea that the evaluations should be performed by an independent organization, which means that laboratory procedures, data processing, and report writing are not handled by the manufacturer's own representatives. Their personnel in each national division are paid with funds from the respective country; the evaluations are financed by the suppliers/distributers of the instruments that are evaluated by the SKUP.[9]

SKUP evaluations follow general guidelines. The evaluation procedure of, e.g., BG test systems is based on ISO standard procedures with certain modifications. The SKUP reports are published at their homepage: www.skup.nu. The supplier/distributor has the opportunity to make comments on the report, along with the response from the SKUP. Considering standardized and independent evaluations of DDTD, the SKUP is probably one of the most established and experienced institutions in Europe.

Tasks for an Independent Institution for the Evaluation of Diabetes Diagnostic and Therapy Devices

From our point of view, the primary task of such an institution is to perform standardized evaluation and comparison of the quality of DDTD after the CE marking process. The outcome of this evaluation should have an immediate impact on the reimbursement policy for these devices. Secondary, the proposed institution can support the work of the notified bodies during the CE marking process.

The exact procedures employed by this institution must be described in detail in standard operating procedures. Complete evaluation results of each evaluation should be published on the homepage of the institution immediately after finishing it. Absolutely mandatory is full transparency in data management and in financial aspects. The quality of the work should be monitored by an independent board of scientists, manufacturers, representatives of people from the health care system, and people with diabetes.

Legal and Financial Considerations

As the structure of the proposed institute becomes clearer, two topics will also have to be considered in detail:

- legal issues (on a national and EU-wide level) and
- Financing, considering European or even national legacies.

In order to work independently, the institution will require payments within a legal framework from all companies requesting an evaluation as well as from the health insurance companies. In order to establish such an institution and to guarantee its existence regardless of volume of evaluations, the manufacturers of DDTD, in general, should provide basic support. However, in light of the fact that health insurance companies have a vital interest in learning which DDTD fulfill certain quality requirements and their high interest in reducing the costs for DDTD, they should also contribute financial support. Health insurance companies have been complaining about the lack of high-quality scientific data for DDTD, but when it comes to covering the costs of such studies, they have stated that these should be financed by the industry.

The costs for the evaluations performed by such an institution will clearly increase the costs of a given medical device to some extent. However, in view of the potential risks, combined with insufficient quality of DDTD, this appears to be a smaller consideration. A cost/benefit analysis should also include the potential of cost savings due to the risk reductions from detecting and removing insufficiently performing DDTD in time.

It is somewhat annoying that financing such an institution is a topic at all. Assuming that the costs for its work will be in the range of few million Euros per year, this is in sharp contrast to the economical relevance of DDTD in the EU. To our knowledge, the costs for reimbursement for BG test systems, insulin pens, and pumps are in the range of several billion Euros in the EU each year.

Summary and Outlook

The work of this institution should not be regarded as a replacement for the CE mark or as a criticism of the notified bodies; however, it should add diabetes know-how and focus more on the impact that unacceptable DDTD might have on people with diabetes.

We regard the outcome of the evaluations as an additional clinically relevant piece of information. Adapting the quality evaluation models that are available (e.g., the SKUP in Scandinavia) and adjusting these to the needs of an EU institution would reduce the time needed to establish this. It would be ideal if the proposed institution can work under the auspices of an academic organization such as the European Association for the Study of Diabetes.[10]

At first glance, the DDTD manufacturers might oppose establishing such an institution and consider it as a new bureaucratic and costly hurdle to obtaining and maintaining market access; however, if they accept that documented quality is not only an important marketing argument but might also allow for price differentiation in the market, then they will find a way to benefit from the work of the proposed institution. It is clear that such an institution should not represent a barrier to market access, especially not for smaller manufacturers. Establishing such an institution will only have relevance when the evaluations have a practical impact, for example, on the reimbursement policy of health insurance companies. Although it will be a time-consuming and difficult task to establish such an independent institution; we should not wait. We see the pressing need to have such an institution in the near future.

Disclosures:

Lutz Heinemann advises medical device companies such as Roche Diagnostics and Sanofi in the development of new diagnostic approaches to diabetes therapy; is a shareholder and consultant at Profil Institute for Metabolic Research, Neuss, Profil Institute for Clinical Research, San Diego, CA; and is one of the two chairs of the Working Group for Diabetes Technology of the German Diabetes Association. Guido Freckmann is the medical director and general manager of the Institute for Diabetes Technology Research and Development GmbH at the University of Ulm, which carries out studies testing BG meters and different studies evaluating devices for diabetes therapy on behalf of various companies, and he holds the other chair of the Working Group for Diabetes Technology of the German Diabetes Association. Theodor Koschinsky advises medical device companies such as Roche Diagnostics and Bayer in the development of new diagnostic approaches to diabetes therapy.

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