Comments on the "Application for inclusion of pen devices and cartridges of human insulin for children and adults with diabetes in the WHO Model List of Essential Medicines (EML and EMLc) (April 2023)", submitted by Kim Donaghue et al.

The technical unit does not support the application "Application for inclusion of pen devices and cartridges of human insulin for children and adults with diabetes in the WHO Model List of Essential Medicines (EML and EMLc) (April 2023)". The application was not developed in consultation with this WHO department.

The stated purpose of the application is "Addition of reusable insulin pens and cartridges and prefilled disposable pens to the EML and EMLc for subcutaneous administration of human insulin in addition to the current insulin vials which require syringes for insulin administration".

Applicants cite the inclusion of long-acting insulin analogues in the 2021 EML and EMLc (*Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen*) highlighting the necessity to use a device (either a reusable pen with insulin cartridges or a pre-filled pen which is discarded when empty). They explain that short-acting and intermediate-acting human insulins in the EML and EMLc are only included as vials (*Injection: 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial*) referring to section 18.5.1 of the EML and EMLc. According to the applicants this implies the use of syringes and argue that human insulin in cartridges and prefilled pens should be listed on the EML and EMLc to eliminate bias "introduced between the two types of insulin (human and analogue) based on different sets of devices for delivery" and to standardise the presentation of existing medicines.

With regard to a potential 'bias' due to different devices for insulin delivery it should be noted that the inclusion of long-acting insulin analogues in the EML and EMLc itself introduced 'bias' because the named injection only referred to cartridges or pre-filled pens, whereas long-acting insulin analogues manufactured in vials are available. Consequently, applicants should also postulate the inclusion of long-acting insulin analogue vials in the EML and EMLc.

In their review of benefits of insulin pens applicants mainly denominate better accuracy not requiring good dexterity and vision, higher patients' acceptance and adherence resulting in improved diabetes control and less hypoglycaemic episodes. Better acceptability in public places and reduced education time on how to deliver insulin are mentioned as additional advantages.

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The applicants specify a “review of Cochrane, Medline, UpToDate, BMJ Best Practice, UK NICE and ISPAD Guidelines”. However, neither search strategies nor results of the search in a flow diagram are provided.

Therefore, the body of the application evidence is mainly based upon two systematic reviews (1,2 – for individual studies see below ‘data on costs’) and two observational studies ((3) with higher use of insulin analogues among pen users, and (4) with type of insulin not reported).

The first systematic review (1) included a total of 17 studies of mixed design with only four studies reporting some data on human insulin. Six studies had a bias-minimising randomised-controlled cross-over design. Of these, three studies only actually evaluated human insulin: *Coscelli 1995* studied 60 mainly type 2 diabetic patients over six weeks. There were no differences in hypoglycaemic events and no significant difference in HbA1c. Most patients preferred the pre-filled insulin pen device. *Kadiri 1998* initiated insulin treatment with pens or vials in 96 type 2 diabetic patients with a follow-up of 12 weeks. There were no differences in glycaemic control nor differences in hypoglycaemic events. Most patients preferred pens, mainly due to easier use, less injection pain and better drawing up insulin dose. *Shlemet 2004* included 79 patients with type 1 and type 2 diabetes with a follow-up of 12 weeks. The mean age was 68.2 years with individuals having visual and/or motor disabilities and difficulties (or required caregiver assistance) for previous injections by vial/syringe. At the end of the study 53% could independently use pens versus 20% vials, and 82% of the patients preferred pens.

Furthermore, applicants identified one study with a total of 65 participants on health-related quality of life (5) favouring pens/cartridges in the summary scale of physical components but not mental components in the SF-36 questionnaire which was significantly higher in the insulin pen group than in the syringe group: the change in the insulin pen group was +3.9 versus -1.0 in the insulin vial group (P = 0.037), reaching a minimal important difference of two to three points in the summary scale of physical components. However, there was a strong risk of bias in this open-labelled, non-randomised clinical study because study participants receiving subcutaneous insulin-injection switched from syringe to insulin pen as suggested by their physicians, therefore introducing selection bias.

With regard to **data on costs** applicants described two publications reporting retrospective analyses of databases (6, 7) and specified “costs savings with use of pens/cartridges, largely due to reduced hypoglycaemia in individuals using Pen/cartridges compared to those using syringes/vials”. However, the only publication describing hypoglycaemic events (7) was a longitudinal, retrospective analysis of the MarketScan and IMS LifeLink health plan claims databases investigating the insulin analogue aspart, therefore not providing relevant information on human insulin.

The other publication (6) was a retrospective analysis of Medicaid-enrolled patients diagnosed with type 2 diabetes mellitus in North Carolina, USA. Comparisons included the following cohorts: (comparison 1) patients with type 2 diabetes mellitus on insulin therapy delivered by vial/syringe who converted to insulin pen therapy versus those who remained on their vial/syringe therapy; and (comparison 2) patients with type 2 diabetes mellitus on an oral antidiabetic medication regimen who initiated insulin (human or analogue insulin) delivered by vial/syringe versus those who initiated insulin pen therapy. Adequate propensity-score statistics to control for confounding bias could only be employed for patients who switched from syringe to pen (n = 560), pair-matched with those who remained on syringe therapy (n = 560). In the analysis of insulin initiation, patients who started insulin therapy (insulin-naive, first-time users) with vial/ syringe (n = 1162) were compared with the cohort who started insulin treatment with a pen (n = 168). Here, propensity-score statistics could not be used due to the small sample size. For comparison 1, total health care costs excluding prescriptions in year two were comparable for patients who converted from a syringe to pen device ($11,476) and those who remained on syringe therapy ($10,755). A cost reduction was observed in syringe-related resource use after conversion to a pen (from $670 to $535). The number of days with syringe use was substantially reduced in patients who switched from syringe to pen therapy. Total health care costs in year one in the matched group design (excluding prescriptions) showed a median for the syringe to pen group of $3525 and for the syringe only group of $3504.

For comparison 2, patients in the pen group were found to have considerably lower overall health care costs excluding prescriptions in year two ($14,857) than those in the syringe group ($31,764). According to study authors “These cost reductions were reflected predominantly by significantly lower total hospital costs ($1195.93 vs $4965.31, respectively; P <0.05), total diabetes-related costs ($7324.37 vs $13,762.21, respectively; P < 0.05), and total outpatient costs ($7795.98 vs $13,103.51, respectively; P < 0.05).”

Regarding adherence, for comparison 1, the diabetes-related medication adherence rate (MPR) for patients who switched from syringe to pen was significantly lower than for those who remained on syringe therapy (45% vs 56%, respectively; P < 0.05). For comparison 2, no significant difference was found in the diabetes-related medication adherence rate for the syringe group (50%) and the pen group (53%).

This study can be criticised on several grounds (as partly indicated by study authors): (1) the retrospective observational study design does not permit causal inferences about the results; (2) external validity of this study is limited because the data were collected from a health care setting in a single US geographic location; (3) authors used the number of injections prescribed to measure insulin

adherence and could not adjust for dosage or time of injections because these data were unavailable; (4) the study lacked data to evaluate associations between sociodemographic characteristics, behavioural predictor variables and clinical outcomes with medication adherence/health care costs; (5) specific reasons for patients to switch from vials to pens could not be evaluated, and (6) the syringe group included older patients with more hospitalisations, more emergency department visits and more outpatient visits.

Therefore, the results of this study have to be interpreted with great caution and cannot be used as a justification to hypothesise that using pen devices results in decreases in health-care service utilisation, prescription costs, outpatient costs or diabetes-related health-care costs.

Furthermore, applicants referenced two surveys (8, 9). The first survey (8) in 13 low-income and middle-income countries did not provide specific data for insulin pens but emphasised the complex mark-up situation for insulin prices in various countries. The second review (9) describing higher costs for pens compared to vials did not report "national daily wage (NDW)" as applicants state but the "International comparison of affordability of insulin products for a least-paid unskilled public servant in terms of number of days' wages required to obtain a 30-day dose" (table 7 in publication). Also, applicants referring to (9) stated that "this needs to be balanced with the added safety, flexibility and adherence benefits". However, neither safety, flexibility nor adherence benefits were mentioned in the publication.

One more publication (10) was provided by applicants stating: "In a survey of 37 LMIC supported by the Life for a Child Program, 16.7% of young people with diabetes less than 25 years of age were using insulin pens (1). Pens were preferred by 74% of individuals." However, this citation is not correct: the survey was conducted in 2019 of leading diabetes centres in 41 countries supported by the Life for a Child Program. Thirty-seven countries returned the survey, four centres in four different countries did not return the questionnaire. The types of respondents were as follows: 20 national diabetes association chiefs, five diabetes nongovernmental organisations doing extensive work in diabetes care, seven government hospitals, two senior endocrinologists, two Ministry of Health officials, and one mission hospital. As reported in the publication, 74.3% (n = 26) of respondents indicated that patients preferred pens, 20.0% (n = 7) syringes, and 5.7% (n = 2) both. Most respondents (74.3%, n = 26) noted that young people experience feeling stigmatized when injecting their insulin with syringes in public. Therefore, the results of this survey related to opinion makers but not to individual patients.

Another important concern, not addressed in this application is the undesirable environmental impact of pre-filled pens (plastic).

Conclusions

The application for inclusion of pen devices and cartridges of human insulin for children and adults with diabetes in the WHO Model List of Essential Medicines (EML and EMLc) (April 2023)", submitted by Kim Donaghue et al. shows substantial deficits:

- The body of evidence is insufficient. Applicants should have developed and reported adequate search strategies to better cover existing studies on the topic and establish their own systematic review. For example, a recent review (11) reported on six randomised-controlled trials not mentioned by the applicants and also on five randomised-controlled trials on prefilled insulin injectors. There are also (systematic) reviews on the topic not mentioned by the applicants (e.g. 12). Therefore, applicants' referenced evidence appears highly selective.
- The applicants did not distinguish between data on human insulin and analogue insulin. This approach made it necessary to investigate every single study reported in the application. Only studies comparing human insulin pens and vials should be included. Even comparing two long-acting insulin analogues both applied by means of pen devices showed differences in glycaemic control, persistence and adherence as well as health-care costs (13).
- A significant percentage of the applicants' included studies are observational studies with an inherent risk of confounding bias making it impossible to clearly associate effects with cause.
- No adequate cost-effectiveness/utility/benefit analysis on the topic appears to be available.
- With regard to disposable pens it is a fact that these are not environmentally acceptable, creating a global problem (14). Data from one small study from Bosnia and Herzegovina showed that only in this small country there were 3.2 million pens used and dispensed annually (15).
- It is possible that many individuals with diabetes prefer using an insulin pen due to its simplicity and convenience. However, there may be significant cost differences between insulin pens and vials.
- Finally, applicants' "Evidence Table" is biased: data on people with type 1 diabetes are scarce, therefore patient/population mainly relates to type 2 diabetes. Advantages of better glycaemic control and less hypoglycaemic episodes (referenced to systematic review (1)) with regard to human insulin were not reported.

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