EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2015
EMA/352689/2015
Pharmacovigilance Risk Assessment Committee

Overview of comments received on 'Risk minimisation strategy for high strength and fixed combination insulin products, draft addendum to the good practice guide on risk minimisation and prevention of medication errors' (EMA/686009/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Dr Keith A Sands, South West Yorkshire Partnership NHS Foundation Trust
2	Dr Roberto Frontini, Universitätsklinikum Leipzig
3	Hampshire Medicines Safety Group
4	North Somerset Clinical Commissioning Group
5	Joanna Bushnell, Medicines Optimisation Pharmacist on behalf of North of England Commissioning Support Unit Medicines Optimisation Diabetes group
6	Standing Committee of European Doctors / Comité Permanent des Médecins Européens (CPME)
7	Association of the Austrian pharmaceutical industry (PHARMIG)
8	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
9	European Federation of Pharmaceutical Industries and Associations (EFPIA)
10	Healthcare Improvement Scotland
11	Medicines Evaluation Board, the Netherlands
12	French National Agency for Medicines and Health Products Safety (ANSM)
13	The European Association of Hospital Pharmacists (EAHP)
14	Piera Polidori, Society of Hospital Pharmacists (SIFO)
15	Pharmaceutical Group of the European Union (PGEU)
16	Guild of Healthcare Pharmacists

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

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1	I am delighted to see that the EMA is developing advice in order to help to minimise medication errors with the increasing number of non-U100 insulins. This will be extremely helpful. However, your draft document does not appear to include U500 insulin, which has been in use in the UK for some years, extensively in some areas. Initially, it was Novo Nordisk who supplied Actrapid U500 insulin but, when they withdrew it in 2008, it was replaced by the Eli Lilly product, Humulin R. Clearly, the possibility of medication errors is of particular concern with this preparation, but there are also issues over its pharmacokinetics/ pharmacodynamics that are apparently not a problem with some of the other more concentrated insulins (eg U200 insulin lispro). Medicines management departments also tend to regard it as different to U100 insulin and classify it as 'for specialist use only', although I imagine this is not relevant to your review. I hope that it will be possible to include U500 Humulin R insulin in your review.	
2	Good practice guide on recording, coding, reporting and assessment of medication errors and Good practice guide on risk minimisation and prevention of medication errors as well as Risk minimisation strategy for high strength and fixed combination insulin products, addendum to the good practice guide on risk minimisation and prevention of medication errors are useful documents and fulfill the scope. The addendum to insulin contains the remarks already made. Nevertheless I strongly suggest adding to the documents a list of the used abbreviations. Some of them are common, some are explained but unfortunately not all. Abbreviations are useful but – as remarked in the text – can also be misleading if not clear.	
3	The Group welcomed this strategy and is in support of the recommendations made within the document.	
4	Fixed combination insulin products – it states each dose step is one unit of insulin. I am concerned that this may increase the risk of an over or under dose of the non-insulin product if patients are used to altering their insulin dose. Dosing based on the non-insulin product would reduce this risk and ensure the product stood out from insulin products.	

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	One dose step = one unit of insulin is not stated in table 5: key safety messages for fixed combination insulin products addressing the risk of medication errors.	
9	EFPIA welcomes the initiative of the draft risk minimization strategy for high strength and fixed combination insulin products with the aim to pro-actively address the risk of medical errors.	
9	The risk of medication errors does not exist only with high strengths insulins although it is more important since the approval of these insulins. The risk minimization activities described in this document might be applicable to any strength of insulins.	
9	The document is written with a focus on pre-filled injector devices and high strength. EFPIA believes flexibility is needed as devices are developed to meet the needs of different patient populations. It is proposed that the guidance could be reworded to emphasise the need for error-proofing and differentiation to prevent dosing errors rather than mandate that development be limited to a single type of device and to high strength.	
9	It is important that the individual Member States should not decide additional need for risk minimisation – This would not be in accordance with the principles behind the European Medicines Agency and the Pharmacovigilance Risk Assessment Committee	
9	Since the guide refers also to devices, it would be highly recommended to made reference to some ISO guide (e.g. ISO EN14971; EN IEC62366).	
9	Suggestion to add a list of abbreviations as there is a numerous of abbreviations.	
10	Overall support of this risk minimisation strategy but some key issues as detailed below from a NHS Scotland perspective.	
11	ANSM proposes to clarify for whom this guideline is intended for: for marketing authorisation holders (MAH) or applicants, for healthcare professionals and/or patients. Furthermore, for applicants, when requesting a MA, a check list for all measures available to minimize risk could be proposed. The guideline could be reorganized as follows : 1: Scope	

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	2: Potential for medication errors 3: Routine risk minimisation - 3.1 recommendations for applicants/MAH - 3.1.1 Drug product design - 3.1.2 Naming and pack design - 3.1.3 SmPC - 3.1.4 User testing - 3.2 recommendations for healthcare professionals and patients 4: Additional risk minimisation measures - 4.1 Conditions or restrictions with regard to the safe and effective use - 4.2 Effectiveness measures 5: Recommendations for clinical management and storage	
13	EAHP welcomes the opportunity to give comment to the EMA on its guidance on risk minimisation strategies for high strength and fixed combination insulin products. Given the known risk of patient fatality from insulin overdose it is critical for health systems that the most appropriate risk minimisation strategies are both identified and put in place. Overall, the draft contains sensible and proportionate advice on measures to reduce risk, and we particularly welcome the emphasis on good practice in pack design and naming. It should be clear to all users from the packaging that the product is high strength. In view of the potential for patients affected by diabetes to also be impacted by visual impairment, EAHP counsels that particular attention also be given to the size and clarity of font on the packaging and pen. An additional measure for risk minimisation that the PRAC should give consideration to, in respect of product and pack design, is the inclusion of an identifying 2D data matrix bar code on the pen. For hospitals that employ bedside scanning to conduct a final check of right medicine, right patient, right dose, right time, right route of administration, such a bar code is invaluable in enabling this check to be conducted.	

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	EAHP strongly support the identified need for healthcare professionals (prescriber, nurse and/or pharmacist) to counsel the patient about the key differences in short and long acting insulin products. EAHP also supports high strength insulin or fixed combination insulin being manufactured in pre-filled pens **only** (e.g. no vials or cartridges). EAHP also raises the issue of individualised labelling of insulin pens. Ideally pen design should permit the placing of patient inscription and other safety information (such as date of opening) to be attached to each pen in the hospital setting, without compromising other features of the device. Finally, EAHP suggests further risk minimisation material be produced to support the introduction of higher strength insulin such as guidelines for use in the hospital setting, a check list when prescribing insulin, a checklist when dispensing insulin preparations.	
15	Our only point here is that at what stage might it be considered that the product is too problematic? With a high error rate perhaps its license should be reviewed.	
16	Could include advice about storage i.e. once in use insulin should be stored at room temperature not in the fridge. Also what about encouraging self-administration in hospital where ever possible.	

2. Specific comments on text

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
3	171	On page 12, first column in table after header, the wording implies switching occurs only one way when it could occur either way. Make wording consistent with that used in tables 3 and 4	Medication error associated with switching BETWEEN conventional insulin AND fixed
5	143	With regard to preventing medication error due to mix up between long acting and short acting insulins:	Could manufacturers add the duration of action of the insulin to the label?
6	151 (table 3)	The table 3 should include a focus on the long term storage (cold) of insulin products at patients´ home	
6	99	The guide should consider the eventual use of (high strength) insulin in hypo kaliemia. Use of insulin without additional glucose has caused deaths in EU.	
6	99	The guide should take into consideration that patients in hospitals and nursing homes have name labels on their pen devices – hiding part of the colour coding.	
6	99	The MAHs should agree on suffixes and colour codes to indicate mix/long term, etc.	
7	123-129	"Pack design and labelling ensure that the critical information necessary for the safe use of a medicine is legible, easily accessible and that users of medicines can easily assimilate this information so that any risk of confusion and error is minimised. The information which should be included on the labelling and package leaflet is provided in Title V of Directive 2001/83/EC. In addition, the details on the display and readability of such information on the printed materials are included in the guideline on the readability of the labelling and package leaflet of medicinal products for human use (hereinafter 'readability guideline')."	

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		To point out the responsibility of other departments than PHV (e.g. Legal, Regulatory Affairs, Marketing, etc.) we strongly recommend to extend and amend other than PHV-relevant guidelines with this information.	
7	144, 148	'Package leaflet (PL)' vs. 'PIL'	Abbreviation for package leaflet and package information leaflet >> please use a consistent language for better readability
7	172	5. Additional risk minimisation measures This paragraph should be completed with a hint regarding Module XVI and its Addendum I	
8	97	The table list of potential medication errors are also included other scenarios. Therefore the heading should be changed.	Potential medication errors to be considered for insulin containing products
8	142-143	The list of potential medication errors are also included other mistakes and therefore the header should be revised in general manner.	Recommendations on naming and pack design of insulin containing products addressing the risk of potential medication errors
8	143 (Device)	Additionally, if cartridges containing long-acting insulin would only fit in specific pen for long acting insulin (marked as such by colour) but not on pens for short acting insulin this would clearly be more helpful in avoiding medication errors especially for visually impaired patients than other appropriate measures.	
8	151-152	The list of potential medication errors are also included other mistakes and therefore the header should be revised in general manner.	Medication error related safety messages in the product information of insulin products
8	170	The list of potential medication errors are also included other mistakes and therefore the header should be revised in general manner.	Key safety messages for insulin products addressing the risk of medication errors
9	50-52	Here it is mentioned that the need for risk minimisation could vary across the different Member States – this should not be the case	One set of risk minimisation across Member States

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9	62-64; 101; 103; 118	If, pre-filled pens only are considered as part of assumptions, it should be valuable to specify as from here why other forms such as vials or cartridges are not considered.	
9	62-64; 100-104;	We believe that dedicated pump/cartridge combinations should also be supported as long as appropriate mechanical or software/hardware guarantees the dedicated combination and simple patient interface (such possibilities might also be applied to reusable pens). The same notion is reasonable for vials if the transfer system into traditional pump reservoirs can be dedicated to that function and restrict vial use with syringes. We support continued use of currently available concentrated insulins in vials where there is a dedicated syringe and unique patient population needs (e.g. insulin resistance) Environmental concerns might favour vials over prefilled pens in special circumstances. We do not support future concentrated insulins in vials unless there is a dedicated syringe and the following considerations (otherwise, we support the exclusion of concentrated insulin vials): a. Dedicated patient populations (e.g. U500) with specific issues like insulin resistance b. Existing patients that fully understand how to dose with concentrated insulins and have done so for quite some time c. For some users, significant or prohibitive cost differences between vial and prefilled pens or pumps d. Environmental objections to prefilled pens given that empty prefilled pens (absent needle) are typically discarded in	"The high strength insulin or the fixed combination insulin product is manufactured in prefilled pens ~~only~~ unless there is a special circumstance."

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		commercial/home waste, which is consistent with most government regulations addressing disposal of empty pens	
9	70	If bioequivalence is not achieved but therapeutic equivalence is, then additional risk minimisation is not needed.	'If bioequivalence cannot be achieved and the product cannot be judged therapeutically equivalent, the applicant should consider additional risk minimisation measures in line with the provisions in chapter 5.'
9	72-75	EFPIA agrees that the pen should reflect the number of insulin units to be administered. Many prefilled insulin pens have an audible and tactile click when the user is dialling the dose; however, the labels warn patients not to set their dose by counting clicks e.g insulin product Tresiba® has one concentration which delivers 2 units of insulin per click. EFPIA believes users may have the option to adjust dialling doses with different audible and tactile clicks for different products. (For instance, Humulin R U-500 pen delivers 5 units of insulin per click and our Humalog Half-Unit pen delivers 0.5 unit of insulin per click). The dial should always display the dose that is being set and ultimately delivered to the patient. Our recommendation is, the dose display must reflect the insulin units. For fixed combinations of insulin and another injectable blood glucose-lowering agent the draft guidance must ensure a definition of what is meant by a 'dose step' as it also appears in Table 5 (line 171), which states that manufacturers should provide an 'Explanation of one dose step of <PRODUCT >. EFPIA does not agree that every prefilled pen should follow the rule of 1 dose step = 1 click = 1 unit of insulin. (refer to comment on line 111-113).	For products where insulin is combined with another injectable blood glucose-lowering agent in a prefilled pen, ~~the number of 'dose steps' is always equivalent to the number of units of insulin to be administered, i.e.~~ the dose counter window on the pen will display the number of ~~dose steps and this will be the same as the number of~~ units of insulin.

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9	90 (Section 2)	The addendum should differentiate between higher concentrations and different strengths of specific formulations. Some insulin products are available in more than one strength or concentration and this should not be changed	
9	94-96	It seems unusual to have to justify why applicable all medication errors listed in Table 1 are not listed in the PV table for safety concerns.	Marketing authorisation holders or applicants should consider ~~provide a justification for any of~~ the potential medication errors listed in table 1 ~~not being addressed as a safety concern in the EU Risk Management Plan~~ in the development of routine and non-routine risk minimisation measures.
9	97 (Table 1); 142 (Table 2); 153 (Table 3);	All These examples of potential medication error are not specific for high strength insulins – e.g. 6th medication error - Needle blockage due to non-compliance with the instructions for use is not a medication error or in any way related to strength of the product but rather to 'product use issue' according to MedDRA.	To distinguish in the table the medication errors specific to high-dose or fixed-combination if any and others which are common to all insulins.
9	97 (Table 1); 142 (Table 2); 153 (Table 3);	List the same potential medication error category in each table. Table 1: Medication error due to non-compliance with instructions to use a new needle for each injection: this can lead to blockage of needle and subsequent injection of wrong dose, differs from Table 2, Table 3 Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle	Adjusted Table 1 with: Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle
9	97 (Table 1); 153 (Table 3);	Needle blockage due to non-compliance with the instructions for use is not a medication error or in any way related to strength of the product but rather to 'product use issue' according to MedDRA.	

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	170 (Table 4);		
9	97 (Table 1)	Eight medication error listed "other safety concerns related to medication errors as applicable" would be more comprehensive if completed by examples.	
9	97 (Table 1 - Item 4);	Fourth medication error Even if the change from high concentration to low dose concentration doesn't have the risk of hypoglycemia, there is the risk of loss of glucose control if the patient is under dosed with insulin (specifically in T1DM). Suggestion to add "vice versa".	Medication error associated with switching patients between standard 100 units/ml and higher units/ml strength insulin products and vice versa.
9	99 -121	For some insulin formulation higher concentration make it possible to give higher number of units in one injection which is regards positive for patients with a high insulin need. Also it is expected that future product will be for once weekly administration or even be with longer intervals between injections. Different pen systems have different dose and dose increments. Normally from ½ to 2 units. This serves different need from different patient pools and is important in for daily clinical use. By correct use of the pen the patient will get the correct dose. It is important that patients do not count clicks but use the dose counter window which displays the dose in units irrespectively of the strength. Other measures based upon a risk management process compliant with ISO EN 14971 are likely to be effective.	
9	101	No need for the 'multiple-dose'. There could be future high insulin strength in single use pre-filled devices.	Delete 'multiple-dose'
9	103-104	If the containers in-use time is shorter than the total usage of the pen the insulin injector device should not be discarded	Proposed change (if any): "The insulin injector device should be discarded when the insulin container is empty, unless if the containers in-use time is shorter

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			than the total usage of the pen."
9	106	'Enable repeated dispensing of fixed doses' indicates that fixed dose rather than flexible dosing is mandated.	…'may enable repeated dispensing of fixed and flexible doses'…
9	110	Pens are used by a multitude of patients, from small children who require small doses to very large adults who may require high doses of concentrated insulins. It is not practical to set a specific maximum for a pen to prevent overdose given the variety of patients who will use insulin pens. This text should rather focus on the manufacturer's responsibility to, through a proper risk management process, compliant with ISO EN14971 to ensure a low and acceptable risk of overdose.	~~The maximum insulin dose per injection should be limited to avoid serious overdose~~. "Insulin products are designed to fulfil the therapeutic needs of different patient populations. Efforts should be made to establish robust differentiation to avoid accidental overdose."
9	111-112	There are marketed products with pre-filled pens with the same active substance where the suggested text does not fit; these products are used by many patients. Propose change: If this is not met - include a sentence in the SmPC to describe this in section 4.2 and in the PIL section 3	
9	111-113; 116 – 117;	We do not agree that 'dose steps' should be the same for all strengths. We agree that the dose counter window should display units of insulin. We do not support the limitation of restricting pen function to 1 unit of insulin for each click of the dose dial. This is problematic for a number of reasons: 1. Restricts innovation by only allowing prefilled pens to last longer a. May increase insulin waste as a function of in-use dating. b. Reduced dose accuracy at lower doses due to increased number of units for same volumetric accuracy (depending upon concentration: U200, U300, and U500) 2. Excludes a more beneficial use of concentrated insulin; facilitating larger max dose settings by increasing dose dial increments (e.g.	Proposed change (if any): ~~For pre-filled pens where the same active substance is available in different strengths, the dose steps should be the same for all strengths, ie one dose step corresponds to one unit of insulin at 100units/ml, 200units/ml, 300units/ml etc~~. ~~To ensure consistency with existing insulin products, one dose step of a fixed combination insulin prefilled pen should contain one unit of insulin.~~

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		dialling 2 or 5 units per click): a. For basal insulins where larger doses are common, may decrease number of injections for total dose. b. Helps reduce injection stroke distance for larger doses, which can be limited by hand size and thumb reach. Both approaches to concentrated insulins have merit (i.e. pens that last longer and pens that offer larger maximum doses). To not allow both approaches favours convenience of changing pens less frequently to what some might argue is the more important objective; allowing for larger max doses and fewer injections to obtain a desired dose. This is particularly important for basal insulins. In addition devices that administer half units may be necessary and should not be precluded.	
9	135-138;	The guidance states that applicants are encouraged to consider new invented names. We believe that the ability to have 2 strengths for one brand name must be maintained with the appropriate risk minimisation activities in place.	
9	143	It is recommended to be clear on the difference between mix-up and handling errors in line with how it is normally done when preparing mitigations and utility testing's	
9	143 (Table 2)	In order to highlight the warnings in a prominent way, the warnings to be highlighted should be kept to the critical ones e.g. non extraction of insulin from pen to pump. Too many warnings will dilute the effect. <u>First/Second medication error listed –</u> Design features and use of colour - Recommendation on pack design – • The proposal is not in accordance with the IDF (International	

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		Diabetes Federation) colour code which defines the insulin (human insulin) but not the strength http://www.aarogya.com/support-groups/diabetes/insulin-colour-code.html The number of colours available is limited. If two long acting insulins have to choose a colour to differentiate between the short acting insulin and the other strength insulin this doubles the challenge. It should not be necessary to write units in full. If the strength is displayed in a way that the units/ml or U/ml is separated and in a different font/colour. Including units in the multi-language pack reduces the available space to display the more critical information of the strength.	
9	143 (Table 2)	First/Second medication error – Device recommendations on pack design. Whole colour used for the prefilled pen should not be suggested, because strength of colour as a risk control measure, depends on the context of e.g. the pens form, its user interface, other graphical elements, and the differentiation strength of all those elements against the corresponding elements of other pens. A full body colour may be very effective avoiding a mix up with another strength of insulin, but weak in avoiding a mix up of long acting and fast acting insulin. Therefore the text should suggest to rely on a usability engineering process compliant with EN IEC62366 to produce and validate truly differentiating designs, and a risk management process compliant with EN ISO14971 to choose the design that will be related to the lowest overall residual risk. This allows balancing the different mix up scenarios against each other.	

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		EFPIA fail to see that avoidance of extraction from the prefilled pen represents a so severe risk that it needs to be placed on the outer packaging. When shifting from U100 to a higher strength and bioequivalence between the different strengths is not demonstrated, then it could be considered to provide guidance on the outer packaging.	
9	143 (Table 2)	First/Second medication error listed – Device Recommendation on pack design EFPIA do not support avoiding the use of the same colour in light or dark shades. Since this help the patient identifying the actual drug class e.g yellow and orange indicate a rapid acting insulin	Delete example.
9	146 -148	If the medication errors have been designed out or minimised by packaging etc then it is not necessary to have all the safety messages outlined in Table 3 in the SmPC/PIL. This may lead to confusion.	
9	152 (Table 3)	1st medication error – This warning assumes that the patient is using long and short acting insulins. This warning should be less specific and just recommend checking for the correct insulin. Proposed change: • ~~Warning of medication errors where short acting insulins have been accidently mixed up with long acting insulins~~ • Need to always check the label of the insulin pen before each injection to avoid accidental mix-ups between ~~long acting and short acting~~ insulins Fifth medication error related to extraction misuse – It is proposed that 'syringe withdrawal' labelling is ALSO directly on	Labelling outer carton and cartridge holder/pen body section 7 and label section 6.

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		the cartridge holder or pen body as patients discard or loose secondary packaging and PIL/IFU.	
9	152 (Table 3)	Seventh medication error Insertion of qualitative and quantitative composition in SmPC section 2 is not really helpful as long as the strength is given in section 1 and should therefore be avoided.	~~SmPC section 2 and PIL section 6 • Qualitative and quantitative composition per ml solution of product.~~
9	152 (Table 3)	It is not clear how the risk is minimised by highlighting the product strength on the packaging, as this to a degree creates the need to also explain "carefully" that the user should not recalculate the dose. The confusion for the user may, given the weakness of information for safety as a risk control measure, actually create a greater residual risk.	
9	153–162	It is useful to remind the reader of the requirements for user testing. There is a lack of reference to the harmonized standard for usability engineering, EN IEC62366 that in conjunction with the harmonized standard EN ISO14971 Risk Management, through proper application, will ensure acceptable risk, regarding all the risks listed in Table 1.	… should comply with Articles 59(3), 61(1) and 63(2) of Directive 2001/83/EC and should be consistent with EN IEC62366 and EN ISO14971.
9	163-164	Safety messaging to HCPs in addition to labelling should not default to routine risk minimisation – messaging for low risk medication errors will dilute the higher risk medication error messaging.	Safety messaging to HCPs should be driven by data from user testing studies and considered additional risk minimisation measures
9	170 (Table 4)	If there is bioequivalence between different strengths we do not agree that adjustment of doses and timing of concomitant insulins/other medications is needed after switching to a higher strength – it appear contradictory to the clinical situation where no dose-recalculation is needed because the amount of insulin units is the same, only the injected volume is different.	In the column on key safety messages for HCPs and patients how to avoid mix-ups between different products and different strengths, please add that patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using the insulin device.

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9	172 (Table 5)	Statement does not take into account that also a combination drug may be prescribed with a flexible dosing (i.e. adaptation of dose steps). Thus the statement should be removed as anyway" the number of 'dose steps' is always equivalent to the number of units of insulin to be administered".	"~~Prescribers should state the number of dose steps to be injected, and the dose frequency, on the prescription;~~"
9	172 (Table 5)	This section is flexible and allows deviations from some of the four basic assumptions a-d, requiring additional safety messages, but information for safety may sometimes have a low level of effectiveness compared with other risk control measures such as those implemented by design or protective measures. We suggest to mentioning these since they in practice are available for the manufacturer, through the ISO EN14971 risk management process.	
9	191		'Should' should be changed to 'could'
9	217-219	"Marketing authorisation holders should follow the guidance provided in GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators (Rev 1) for effectiveness measures to be included in the EU Risk Management Plan."	Marketing authorisation holders should follow the guidance provided in GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators (Rev 1) for effectiveness measures to be included in the EU Risk Management Plan subject to feasibility.
10	52-54	Strongly supportive of this approach.	
10	62-64; 102-103;	Unsure where the evidence for manufacture of these products in only pre-filled pens comes from. In Scotland the policy is that pre-filled pens are ONLY for patient self-administration; and healthcare professionals will administer to patient from vials and NEVER pre-filled pens. The rationale behind this is that nurses are not trained on all prefilled pen device systems so there is a greater risk of error to the patient if staff who are unfamiliar with the pen devices administer when patients are not capable of self-administration. Additionally	Please review this recommendation in line with the feedback against above.

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		nurses, carers, relatives using prefilled pens risk needle stick injury as insulin pen needles are resheathed prior to detachment from the device for disposal. In the inpatient setting nurses should use a vial and syringe to administer insulin preparations. BD auto shield pen needles have been introduced in some health boards - in Dumfries these are currently used with devices by nurses to administer insulin so there is a risk that nurses will use these new devices. General nurses will not have the experience to familiarise themselves with the different mechanisms of all the devices on the market. If this recommendation were adopted then it would be a major policy change in Scotland that would have a staff education resource attached. As well safety needles would need to be purchased for use in the ward areas to avoid needle stick injury risk from the normal pen needles.	
10	187	This identifies a healthcare professional guide for prescribing, dispensing and administering these products, in addition guidance re suitable alternative in should be considered. As these new mixture/high strength products only come in a pen device a suitable alternative would be advised in patients who are not safe/not well enough to self-administer.	
10	142 (Table 2)	Under strength, the recommendation that a minimum font size of 12 should be advocated for readability.	Addition as above.
11	96 (Table 1)	Last row(s). We propose one additional potential medication error.	Add the following potential medication error: Medication error due to not removing the needle immediately after use: this may lead to an underdose due to air in the pre-filled pen. If the needle is left on the pen, expansure/shrinkage of the content of the pen due to

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			temperature changes (e.g. between day and night) may result in entrance of air into the pre-filled pen. This may cause an underdose at the next injection.
11	100–130		Add the type of medication errors which will be reduced by the proposed routine risk minimisation measures.
11	142 (Table 2)	An unclear recommendation is stated for several types of medication errors (unnecessary dose recalculation, misuse related to extraction of insulin from a pen using a syringe, wrong dose injected due to blocked needle), namely "*It is recommended to highlight the warning in a prominent way and on the main panels*".	Include the definition of "main panel" and indicate how much information could be included on a "main panel".
11	142 (Table 2)	1st row, under "Strength" and "Units to be spelled …": 4 U seen as "40" or 4u seen as "44". Such an error in the strength to 10-fold underdose instead of overdose. The same error in a dosing instruction would lead to 10-fold overdose (as correctly stated in table 4)	Change overdose to underdose.
11	142 (Table 2)	1st row, under "Device": we suggest that a palpable mark is added to the colour marking. This is because for healthcare professionals the injection is a routine operation, and feeling the pen contributes to identification of the product, in addition to colour. The Dutch Diabetes patient association often receives messages that only a colour marking at the end of a pen is not sufficient to prevent mixing-up of different pens. This is particularly relevant for health carers in e.g. nursing homes, where several diabetes patients have to be injected. See also below for proposals for corresponding additional safety messages in table 3.	Add: Palpable structure (e.g. ridge or thickening) e.g. half-way the pen next to the cap.
11	142 (Table 2); 169 (Table 4)	If it was intended to mention all potential medication errors included in table 1: tables 2 and 4 are incomplete.	Medication error associated with switching from conventional insulin to fixed combination … should be added.
11	150 (Table	2nd row: "Explain that the product is available in <u>two</u> strengths…."	replace "two" by "two or more different" Use the same

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	3)	However, there may be more than two, as is also mentioned in other parts of the table.	wording in table 4 (twice in 2nd row).
11	150 (Table 3)	Addition of a row with: "Medication error due to not removing the needle immediately after use: this can lead to serious underdose due to air in the pre-filled pen." (see also the comment above).	In the row with: "Medication error due to not removing the needle immediately after use: this may lead to an underdose at the next injection due to air in the pre-filled pen", add: "SmPC section 6.6 and PIL section 3: The needle should be discarded immediately after each injection".
11	150 (Table 3)	5th row: ''…never use a syringe to draw the product from the glass barrel of the pre-filled pen into a syringe".	Delete "use a syringe" or "into a syringe".
11	150 (Table 3)	7th row: should the dose calculation also be explained compared to the mono product of the non-insulin component?	Add comparison to mono product of the non-insulin component, if applicable.
11	150 (Table 3)	SmPC and PL wordings are presented in table 3 for cases when the high strengths are bioequivalent and when no dose recalculation is necessary. However, no text proposals are included for cases of bio-inequivalence and when a dose step is more than one unit, which might be very helpful.	
11	165	It is not clear whether the "key safety messages for healthcare professionals" as described in section 4 are intended as SmPC texts or whether these are meant for additional risk minimisation measures.	Please describe how the key safety messages are intended to be implemented via routine (SmPC PL), additional risk minimisation measures or both.
11	172 (Table 5)	1st row:4th indent: now only the number of dose steps is mentioned. Should it now not be mentioned that the number of dose steps corresponds to the number of insulin units?	Add number of insulin units, if applicable.
11	96 (Table 1)	Last row(s). We propose one additional potential medication error.	Add the following potential medication error: Medication error due to not removing the needle immediately after use: this may lead to an underdose due to air in the pre-filled pen. If the needle is left on the pen, expansure/shrinkage of the content of the pen due to

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			temperature changes (e.g. between day and night) may result in entrance of air into the pre-filled pen. This may cause an underdose at the next injection.
11	100-130		Proposed change (if any): Add the type of medication errors which will be reduced by the proposed routine risk minimisation measures.
12	143	Mention of long- or short-acting insulin on the outer carton and immediate packaging to avoid dispensing and administration errors should be recommended	
12	143	The line concerning Device: ANSM proposes not to mention the device name (such as KwikPen® for all Humalog) on pre-filled pen to avoid confusion with other medicines such as long or short-acting standard or high strength Insulin products that use the same device.	
13	111-113	EAHP strongly supports the recommendation, that one dose step ("a click") should always be 1 unit, independently from the strength of the insulin (e.g.: 1 click of insulin strength 100 units/ml corresponds to volume 0.01 ml, and 1 click of insulin strength 200 units/ml corresponds to volume 0.005 ml). This is especially important for patients with visual impairment, a secondary health complication often associated with diabetes. EAHP advises that this is clearly marked on the primary package using appropriate font size and explained with an example in the PIL and SmPC. It should be also emphasised to healthcare professionals that they should be using number of dose step when counseling the patients about administration.	
13	187-188	EAHP seeks clarification if the proposed healthcare professional guide will be reviewed by the EMA in line with this guidance prior to	

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		publication by the market authorisation holder.	
14	78-79	We suggest to extend the guidelines to all insulin products, to have the same level of safety and standardisation, considering that all insulin products are classified as high alert medications.	
14	100	We suggest that for hospital use only, the high strength insulin product should be manufactured in vials too. In intensive care units short acting insulin products are used for continuous infusions so the vials are more useful for the preparation of insulin drips.	
14	142-143	In the part of the Table “Design features and use colour”, we suggest to have standard European fixed colour codes or pictograms to highlight different strengths or to highlight the different action (for example Long action versus Short Action). In the part of the Table “Device” we suggest to have a label on the insulin pen where to write the patient’ ID (for example name, surname and birth date). This label will decrease the risk of potential exchanges of insulin pens of different patients during the hospitalisation. A second label/specific box it is needed to write the opening date and the end use date according the indication of the manufacturer.	
16	7	Do not like the use of the work error prefer incidents at it reduces the idea of fault and blame when trying to create a learning culture which encourages reporting for learning.	Use incidents instead of errors
16	123	Could the strength be in a red triangle like traffic warning signs? Should it be mandatory that the insulin strength is added to the labelling of all insulins (might be confusing if just those with high strength insulin, may also cause problems for IT labelling systems with limited numbers of characters.	

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16	142	In the table under strength it suggests encouraging strength to be included I think this should be mandated. Also why not include the phrase “short acting insulin” or “long acting “insulin on the packaging.	