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3 Pharmacovigilance Risk Assessment Committee (PRAC)

4 **Good practice guide on risk minimisation and prevention**  
5 **of medication errors**

6 Draft

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8 Comments should be provided using this [template](#). The completed comments form should be sent to [medicationerrors2013@ema.europa.eu](mailto:medicationerrors2013@ema.europa.eu) by 14 June 2015.

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Keywords *Pharmacovigilance, medication errors, risk minimisation, error prevention;*



11 **As part of the public consultation of the draft good practice guide on risk minimisation and**  
12 **prevention of medication errors the European Medicines Agency (EMA) would also like to**  
13 **take the opportunity to obtain stakeholder feed-back on the following questions:**

- 14 1. With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in  
15 harm during the post-authorisation phase useful taking into account the regulatory remit for risk  
16 minimisation measures?

17 **Good practice guide on risk minimisation and prevention**  
18 **of medication errors**

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## 58 **Executive summary**

59 Medication errors present a major public health burden and there is a need to optimise risk  
60 minimisation and prevention of medication errors through the existing regulatory framework. To  
61 support operation of the new legal provisions amongst the stakeholders involved in the reporting,  
62 evaluation and prevention of medication errors the Agency in collaboration with the EU regulatory  
63 network was mandated to develop specific guidance for medication errors, taking into account the  
64 recommendations of a stakeholder workshop held in London in 2013.

65 This good practice guide is one of the key deliverables of the Agency's medication error initiative and  
66 offers stand-alone guidance on risk minimisation and prevention of medication errors, including  
67 population specific aspects in paediatric and elderly patients as well as the systematic assessment and  
68 prevention of the risk of medication errors throughout the product life-cycle.

## 69 **1. Introduction (background)**

70 A medication error is considered to be any unintended failure in the medication process, including the  
71 prescribing, dispensing or administration of a medicinal product while in the control of the healthcare  
72 professional (HCP), patient or consumer, which leads to, or has the potential to lead to, harm to the  
73 patient. Examples of common medication errors include giving a medication to the wrong patient, the  
74 wrong dose of a medication being given to a patient or forgetting to give a patient a medication that  
75 had been prescribed for them. Competent authorities in EU Member States, marketing authorisation  
76 holders and the Agency have a number of obligations as detailed in Title IX of Directive 2001/83/EC  
77 and Regulation (EC) 726/2004, chapter 3, Article 28. These relate to the recording, reporting and  
78 assessment of suspected adverse reactions (serious and non-serious) associated with an error in the  
79 prescribing, dispensing, preparation or administration of a medicinal product for human use authorised  
80 in the European Union (EU), including scientific evaluation and risk minimisation and prevention.

81 Medication errors represent a significant public health burden, with an estimated global annual cost  
82 between 4.5 and 21.8 billion €<sup>1</sup>. Individual studies have reported inpatient medication error rates of  
83 4.8% to 5.3% and in another study, prescribing errors for inpatients occurred 12.3 times per 1000  
84 patient admissions<sup>2</sup>. In most cases medication errors are preventable, provided that the potential  
85 risks of medication errors have been considered during the product development and early marketing  
86 phases (when most medication errors will occur), appropriate measures put in place and reactive  
87 measures taken in response to documented reports of medication error. It is important that reports of  
88 medication errors and interventions are evaluated and incorporated into a continuous quality  
89 improvement (CQI) program.

## 90 **2. Scope**

91 This guidance outlines the key principles of risk management planning in relation to medication errors  
92 arising from the medicinal product (such as those related to the design, presentation, labelling,  
93 naming, and packaging). This guidance describes the main sources and categories (types) of  
94 medication error which may need to be considered, uses real-life examples of such errors, the  
95 measures implemented to minimise the risk of these occurring and suggests proactive approaches to  
96 risk management planning throughout the product life cycle. The recording, coding, reporting and  
97 assessment of medication errors is covered in a separate guidance document.

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<sup>1</sup> [http://www.who.int/patientsafety/information\\_centre/reports/Alliance\\_Forward\\_Programme\\_2008.pdf](http://www.who.int/patientsafety/information_centre/reports/Alliance_Forward_Programme_2008.pdf)

<sup>2</sup> Medication Errors: An Overview for Clinicians Wittich, Christopher M. et al. Mayo Clinic Proceedings , Volume 89 , Issue 8 , 1116 - 1125

### 98 **3. Legal basis**

99 Directive 2001/83/EC specifies that the definition of the term 'adverse reaction' should cover noxious  
100 and unintended effects resulting not only from the authorised use of a medicinal product at normal  
101 doses, but also from medication errors and uses outside the terms of the marketing authorisation,  
102 including the misuse and abuse of the medicinal product. The risk management system (described in  
103 Directive 2001/83/EC) documents the risks which may be associated with use of a medicinal product,  
104 including those which arise from medication error and any measures which may mitigate these risks.  
105 Commission Implementing Regulation 520/2012 defines the content and format of the risk  
106 management plan, with provision in Part II (the safety specification) Module SVI (Additional EU  
107 Requirements for the safety specification) for a discussion and description of medication errors which  
108 may be associated with the medicinal product.

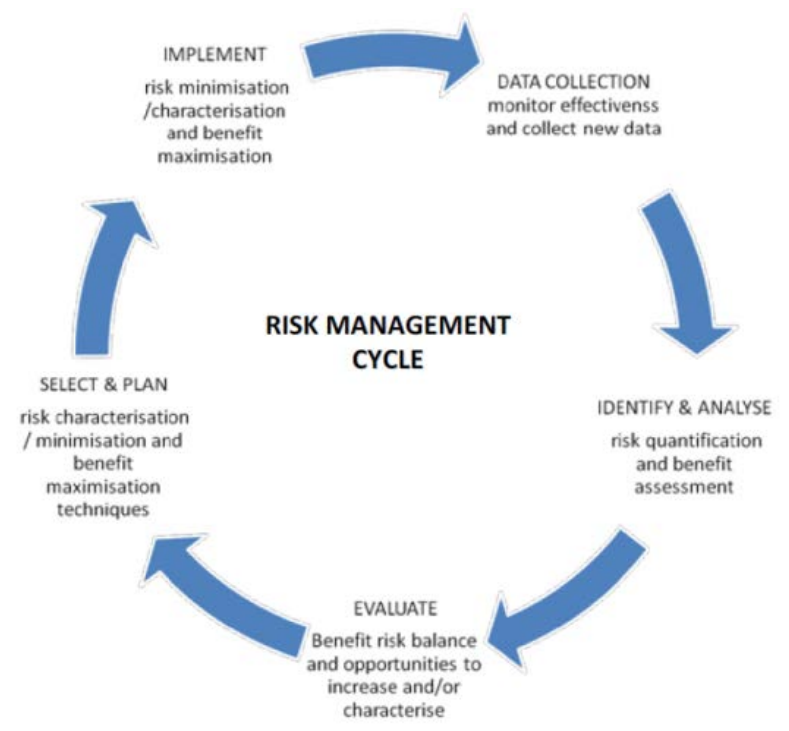
### 109 **4. Definitions**

110 The definitions provided in Article 1 of Directive 2001/83/EC and those provided in chapter 4 of the  
111 good practice guide on recording, coding, reporting and assessment of medication errors should be  
112 applied for the purpose of this guidance; of particular relevance for risk minimisation and prevention of  
113 medication errors are the definitions provided in GVP module V on risk management systems (Rev 1)  
114 which include the general principles presented in the ICH-E2E guideline, and GVP module XVI on risk  
115 minimisation measures: selection of tools and effectiveness indicators (Rev 1).

### 116 **5. Structure and processes**

#### 117 ***5.1. General principles***

118 Good Vigilance Practice Module V describes the general principles of risk management planning, which  
119 is a global process, continuous throughout the lifecycle of the product. It involves the identification of  
120 risk at the pre-authorisation phase, during evaluation of the marketing authorisation application and  
121 post-authorisation phases. It also involves planning of Pharmacovigilance activities to monitor and  
122 further characterise risks, planning and implementation of risk minimisation activities and  
123 measurement of the success of these activities.



124

125 It is vital that risk management planning in relation to medication errors is proactive and begins at a  
 126 very early stage in product development. Medication errors can arise at any stage of treatment  
 127 process, including prescribing, dispensing, preparation for administration, administration and provision  
 128 of information. Such errors can lead to over- or under-dosing, incorrect application via the wrong route  
 129 of administration or administration to the wrong patient population. The consequences may include 1)  
 130 serious adverse reactions including death, 2) an increased incidence and/or severity of adverse  
 131 reactions and 3) loss of efficacy.

132 During the product development process, Marketing Authorisation Holders (MAHs) should consider the  
 133 various sources of medication error, their relevance for the product and the likely impact on the  
 134 balance of risks and benefits. This should take into account relevant products in the same or similar  
 135 indication(s) already on the market. MAHs should consider whether any significance changes to the  
 136 marketing authorisation may increase the risk of medication error. Such changes may include (but are  
 137 not limited to) introduction of a product that differs from an authorised/established product regarding:

- 138 • concentration or strength
- 139 • pharmaceutical form
- 140 • composition
- 141 • method of preparation
- 142 • route of administration
- 143 • different administration device
- 144 • used in a different patient population or indication
- 145 • inbuilt distinguishing features in terms of appearance (e.g. design and appearance of insulin  
 146 pen device).

147 The RMP should be used to document the safety considerations given to product design and should be  
 148 kept updated during the product life-cycle, in a dedicated section which describes the potential for

149 medication errors (GVP V.B.8.6.4 module SVI). This includes a detailed description of medication errors  
150 which may occur based on the product design (including packaging), pharmaceutical properties and  
151 pharmacology of the product, and at all stages: dispensing, preparation for administration and  
152 administration. The RMP should also include aggregated data in the form of a summary of medication  
153 errors identified during the clinical trial programme (and any preventative measures taken as a result  
154 of these reports), the effects of device failure (where relevant) and a summary of any medication  
155 errors reported with the marketed product. Any risk minimisation measures proposed by the MAH to  
156 reduce confusion between old and new “product” (where significant changes to the MA or line  
157 extensions have been introduced) should be discussed in the RMP.

158 When a potential risk of medication error has been identified, medication error should be captured in  
159 the RMP as an important risk and both routine and additional risk minimisation measures may be in  
160 place in place to reduce the risk of medication error. Furthermore, MAHs have an obligation to describe  
161 and discuss patterns of medication errors and potential medication errors within every Periodic Safety  
162 Update Report (PSUR), even when these are not associated with adverse reactions. The context of  
163 product use, including the setting, stage of medication process, category (type) of medication error,  
164 contributing factor(s), medicinal product(s) involved, covariates defining the treated population,  
165 patient outcome, seriousness, mitigating factors and ameliorating factors should be considered and  
166 discussed in relation to these reports. These factors are relevant not only for root-cause analyses but  
167 also for developing appropriate risk minimisation measures.

## 168 **5.2. Assessing the potential for medication errors during the product life-cycle**

### 169 **5.2.1. General considerations for potential sources of medication error**

170 There are numerous potential sources of medication error and it is therefore important to fully consider  
171 and evaluate what errors may arise, at what stage they may occur, whether these are likely to have  
172 consequences in terms of safety outcomes or loss of efficacy and what measures may mitigate the risk  
173 of medication errors occurring. Although some medication errors may occur at the treatment phase,  
174 many of these could be identified at the product design stage, by considering the ways in which the  
175 products will be used and whether there is any potential for error<sup>3</sup>.

#### 176 **5.2.1.1. Product design**

177 Many different designs of medicinal product are available and all may be associated with medication  
178 error. The US Food and Drug Administration<sup>4</sup> has developed guidance on safety considerations for  
179 product design to minimise medication errors; this guidance is complimentary to EU guidance and may  
180 be useful to consider. A high-level overview of the most common sources of medication error based of  
181 the design of product is included in Annex 1.

#### 182 *Medication Errors in the context of the therapeutic armamentarium*

183 It is important to explore the potential for medication errors in the context of the available therapeutic  
184 armamentarium and where a new product may sit within this. This requires an overview of available  
185 treatment options at the EU Member State level and consideration of whether there is the potential for  
186 confusion of mix-ups between products with the same indications due to similarities in posology,  
187 appearance, method of administration, strength or packaging.

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<sup>3</sup> In the UK, the Department of Health has issued guidance on a system-wide design-led approach to tackling patient safety in the British National Health Service (<http://www.edc.eng.cam.ac.uk/medical/downloads/report.pdf>)

<sup>4</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm331808.htm>



## 188 **5.2.2. Typical errors during the clinical trial programme**

189 Subjects in clinical trials are typically closely monitored and have at least semi-regular contact with  
190 study investigators during the trial. This controlled environment may therefore not reflect ‘real world  
191 use’, but even in the clinical trial scenario, medication errors may still occur. One study<sup>5</sup> of cancer  
192 clinical trials suggested the most common type of errors were prescribing (66%), improper dose  
193 (42%), and omission errors (9%). The study found that not following an institutional procedure or the  
194 protocol was the primary cause for these errors (39%), followed by the written order (30%), and poor  
195 communication involving both the healthcare team and the patient (26%).

196 Common sources of medication errors in trials may relate to use of small font sizes and absence of  
197 information on dose/strength in the plain packaging used for investigational products and such factors  
198 are unlikely to impact on the marketed product’s design or presentation. However, the clinical trial  
199 setting may be particularly useful for identifying any difficulties using medicines presented with a  
200 device or as a premixed solution for administration. This may allow for an early indicator of  
201 refinements that may need to be made to the design of the product or instructions for use prior to  
202 labelling, approval and marketing.

203 During clinical trials, it may become evident that some drug product design features increase the risk  
204 of medication errors. In this scenario, Applicants should provide an appropriate risk analysis for  
205 medical errors detected in the clinical trial programme and use this as a basis for refinement in the  
206 proposed pharmacovigilance and risk minimisation activities (or both).

## 207 **5.2.3. Data from “failure mode and effects analysis” and “human factor** 208 **testing” (pre-authorisation)**

209 Successful risk management is based, in part, on effective quality management systems and a number  
210 of tools may be useful in proactively identifying and assessing the risk of medication errors.

211 The FDA guidance on safety considerations for product design referred to in chapter 5.2.1.1.  
212 recommends two tools in particular, “failure mode and effects analysis” (FMEA) and “simulated use  
213 testing” (also known as “human factors” or “usability” or “user” testing). The report of the EMA’s 2013  
214 workshop on medication errors<sup>6</sup> notes the Pharmaceutical Industry’s suggestion to use other methods  
215 of human factor engineering that test how the actual product is used, such as the “perception-  
216 cognition-action” (PCA) analysis, to be carried out early in development.

217 For medicinal products delivered via an administration device, the International Standard for usability  
218 testing for medical devices should also be followed (ISO/IEC 62366: Medical Devices – Application of  
219 Usability Engineering to Medical Devices<sup>7</sup>).

### 220 **5.2.3.1. Failure mode and effects analysis (FMEA)**

221 The Institute for Safe Medication Practices (ISMP) has issued guidance on the principles of conducting  
222 FMEA<sup>8</sup>. Broadly, this involves analysis of all the potential sources of medication error before they  
223 occur, in the situations under which they may occur (e.g. prescribing, dispensing, preparation and  
224 administration). The FMEA proactively considers 1) the processes in each situation, 2) possible failures  
225 (what might happen), 3) the possible causes, 4) the effects on the patients, 5) the severity of the  
226 effect on the patient, 6) the probability the error may occur (which collectively suggest how much of a  
227 hazard is presented) and 7) proposed actions to reduce the occurrence of failures.

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<sup>5</sup> J Clin Oncol (Meeting Abstracts) June 2007 vol. 25 no. 18\_suppl 6547

<sup>6</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/05/WC500143163.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf)

<sup>7</sup> [http://www.iso.org/iso/catalogue\\_detail.htm?csnumber=38594](http://www.iso.org/iso/catalogue_detail.htm?csnumber=38594)

<sup>8</sup> <https://www.ismp.org/tools/FMEA.asp>

228 In addition to errors due to product design (Annex 1), failures may relate to the product name,  
229 labelling and marking with Braille, the presentation of packaging and issues relating to storage of  
230 medicines. FMEA should assess all of these factors.

#### 231 **5.2.3.2. Simulated use testing**

232 There is currently no legal requirement for user-testing of instructions for use or administration or  
233 reconstitution of medicines in order to investigate the potential for medication errors.

234 Applicants who have performed simulated use testing are encouraged to provide the data as  
235 supporting evidence in EU applications. Applicants may also be asked to provide such data if there is  
236 concern over the risk of medication error during the assessment of the application.

#### 237 **5.2.4. Defects and device failure (pre-authorisation)**

238 For medicinal products delivered via device, the International Standard (ISO 14971:2007 Medical  
239 devices - Application of risk management to medical devices<sup>9</sup>) should be followed. Products which  
240 incorporate devices for administration where the device and the medicinal product form a single  
241 integral product designed to be used exclusively in the given combination and which are not re-usable  
242 or refillable (e.g. a syringe marketed pre-filled with a drug) are covered by medicines legislation.  
243 However, in addition to this, the relevant essential requirements in Annex 1 of the Medical Devices  
244 Directive 93/42/EEC<sup>10</sup> also apply with respect to safety and performance related features of the device  
245 (e.g. a syringe forming part of such a product).

246  
247 Some of the medication errors related to medicines administered via devices are described in Annex 1  
248 but these largely relate to errors which may occur even when the medicinal products are within quality  
249 standards or devices are functioning normally. It is also important to consider that medication errors  
250 may arise when a) medicinal products are defective, b) medical devices fail or are found to be  
251 defective (see examples below and in annex 1) or c) patients or HCPs misuse the product. Further  
252 information on the distinction between a product quality issue and a medication error is included in the  
253 Good Practice Guide for the Recording, Coding, Reporting and Assessment of Medication Errors.

254 For medicinal products delivered via device, Applicants should consider the likelihood of common  
255 problems such as blocked or blunt needles, mix-ups between products presented in similar devices  
256 (e.g. low- and high-strength insulins), needles being of an appropriate length to deliver the medicinal  
257 product to the correct site of administration, non-functioning of inhaler devices under normal  
258 conditions of use or after dropping of the device (and other real-life examples encountered in the  
259 context of patient safety incident reporting described in Annex 1 and in the guidance on risk  
260 minimisation strategies for high strength and fixed combination insulin products included as an  
261 addendum to this guidance).

#### 262 **5.2.5. Medication errors resulting in harm during post-authorisation phase**

263 Although the risk of medication errors can be considered during the product design stage and using  
264 data gathered from the clinical development programme, it is not until 'real life' use in the post-  
265 marketing environment that some medication errors will be identified. This may occur at various stages  
266 of the treatment process and involve multiple HCPs and other stakeholders.

##### 267 *Prescribing*

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<sup>9</sup> [http://www.iso.org/iso/iso\\_catalogue/catalogue\\_ics/catalogue\\_detail\\_ics.htm?csnumber=38193](http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_detail_ics.htm?csnumber=38193)

<sup>10</sup> <http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/medical-devices/>

268 A prescription is a written order, which includes detailed instructions of what medicinal product should  
269 be given to whom, in what formulation and dose, by what route, when, how frequently and for how  
270 long. Thus, a prescription error can be defined as a failure in the prescription writing process that  
271 results in a wrong instruction about one or more of the normal features of a prescription. Medicinal  
272 products are most commonly prescribed by physicians but can also be prescribed by other HCPs with  
273 appropriate training including nurses, dentists, pharmacists and optometrists. It is therefore important  
274 that all such HCPs are aware of the errors that may be introduced at the prescription stage.

275 Prescribing errors may relate to stipulation of the wrong drug, dose, strength, indication, route of  
276 administration/pharmaceutical form or length of treatment. Medicinal products with a narrow  
277 therapeutic window or which are toxic in overdose may be particularly associated with medication  
278 errors if errors in dosing occur (e.g. a patient with chronic back pain developed respiratory failure after  
279 being prescribed oral morphine 100mg MST BD in instead of morphine 10mg MST BD).

280 Medicinal products may not be down-titrated appropriately; a patient developed 'grey man syndrome'  
281 when prescribed amiodarone 200mg three times daily for a month instead of being down-titrated to  
282 200mg daily after a week. In some situations the periodicity of dosing may differ across various  
283 indications, e.g.:

- 284 • cases of methotrexate overdose have been reported in patients who took methotrexate once daily  
285 instead of once weekly for anti-inflammatory purposes and this has led to an update of the label to  
286 state that the medicine should be taken once weekly
- 287 • dose calculation and infusion rate errors have been reported with tocilizumab, which has  
288 indications in rheumatoid arthritis, systemic juvenile rheumatoid arthritis and paediatric juvenile  
289 idiopathic polyarthritis with different doses and infusion rates required depending on the indication  
290 and weight of the patient; educational materials were put in place for patients, nurses and  
291 physicians and patients should be monitored for infusion-related ADRs.

292 It is important to consider situations when immediate-release and slow- or modified-release  
293 formulations are available and in this case the intended formulation should be clearly indicated on the  
294 prescription e.g.:

- 295 • Patients were mistakenly treated with immediate release tacrolimus instead of prolonged release  
296 tacrolimus which in some cases resulted in patients being dosed incorrectly, leading to serious  
297 adverse reactions including biopsy-confirmed acute rejection of transplanted organs. Following  
298 these incidents, HCPs were reminded of the potential for mix-ups and the packaging was amended  
299 to highlight the once-daily dose regimen for the prolonged-release formulation.
- 300 • Incorrect dosing with pramipexole was reported when the immediate-release formulation was  
301 mistaken for the prolonged-release formulation and accidental overdose was reported when  
302 prolonged-release formulations were crushed for ease of swallowing. Packaging was redesigned to  
303 differentiate between the two products and packaging and Package Leaflet for the prolonged-  
304 release formulation carries a clear warning that the medicine must be swallowed whole and not  
305 chewed, divided or crushed.

306 Handwritten prescriptions may introduce errors through use of abbreviations, particularly when  
307 handwritten, (e.g., 'OD' can mean once daily or right eye, 'QD' (once daily) may be misread as 'QID' (4  
308 times a day), 'U' (used as an abbreviation for 'units') may be read as zero, trailing zeroes may be used  
309 so that 1.0mg is read as 10mg). Hard-to-read handwriting, misspelling of drug names and lack of  
310 detail on dose and quantity may also introduce mistakes in prescriptions. The ISMP has previously  
311 published a call to action to eliminate handwritten prescriptions<sup>11</sup> and this focused on eliminating the

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<sup>11</sup> <https://www.ismp.org/Newsletters/acutecare/articles/Whitepaper.asp>

312 use of error-prone abbreviations by healthcare professionals. The widespread use of electronic  
313 prescribing systems generally eliminates such errors. However, it is still possible to select the wrong  
314 drug, dose and quantity from drop-down menus for inclusion in electronically-produced prescriptions.  
315 It is also important that electronic systems can be designed or updated to capture all key areas of  
316 prescribing information, sufficient to minimise errors.

### 317 *Dispensing*

318 Prescriptions are largely dispensed in both hospital and community pharmacies. Errors may be  
319 introduced by selection of the wrong product from the shelf, in terms of wrong drug, formulation, dose  
320 or strength (e.g. a patient with chronic obstructive airways disease was reported to have collapsed and  
321 experienced breathing difficulties when he was prescribed prednisolone 40mg once daily for 7 days but  
322 was instead given propranolol 40mg once daily). Such errors may arise due to similarities in packaging  
323 design, strength not being clearly highlighted and similarities in product name. Where dispensing labels  
324 are used, further errors may be introduced by the dispensing label if these carry incorrect dosing  
325 instructions and there may be inconsistency between the dispensing label and the product supplied  
326 such as drug name, strength or pharmaceutical form.

327 It is also possible that a prescription may be dispensed to the wrong patient altogether, particularly in  
328 the hospital environment or care home. Good practice to avoid such errors could include asking a  
329 patient specifically if the product they have been dispensed is the one they usually get and checking  
330 that it is the product generally recommended in treatment guidelines.

331 It is common for patients to be given medicinal products when discharged from hospital and this may  
332 be another source of error (e.g. a patient who underwent percutaneous intervention was not given any  
333 antiplatelet medication aspirin or clopidogrel and discharge was rushed, meaning that medications  
334 given on discharge were not explained; this patient received no antiplatelet medications for 2 weeks  
335 and was readmitted with blocked stents).

### 336 *Preparation and administration*

337 Some medicinal products for IV use or parenteral administration require preparation, dilution or  
338 reconstitution prior to use and this may introduce medication errors, examples of which are illustrated  
339 below:

- 340 • lack of efficacy was reported with leuprorelin suspension for injection due to errors in the  
341 preparation, mixing and administration of the product, requiring amendment of the instructions for  
342 use/reconstitution.
- 343 • there have been numerous reports of medication error (some fatal) when concentrated solutions of  
344 potassium chloride have been given to patients without first being diluted or if erroneously  
345 substituted for sodium chloride. This has led many national safety organisations to issue  
346 recommendations on the stocking, storage, handling and labelling of concentrations potassium  
347 chloride to minimise these risks.
- 348 • there have been reports of life-threatening overdose with a hybrid formulation of topotecan due to  
349 confusion arising from the hybrid having a higher concentration than the dilution concentration of  
350 other topotecan products; this is clearly labelled in product information and a coloured vial collar  
351 acts as a strong visual reminder to notice the concentration.
- 352 • There have been reports of inappropriate dilution of bortezomib which is reconstituted with  
353 differing amounts of solvent depending on the site of administration; a dosing card, poster, a  
354 leaflet and product information describe the correct dilution for administration by subcutaneous  
355 (SC) and IV routes.

- 356 • Prescribing, dispensing and medication errors have been reported with olanzapine where the  
357 rapidly-acting intramuscular (IM) injection formulation has been confused with the prolonged-  
358 release depot formulation; a HCP awareness programme is in place including a DVD, slides,  
359 brochure and patient alert card to explain the differences between the two IM formulations of  
360 olanzapine (including packaging differences)

361 A product presented as two ampoules (one containing water as the solution for injection and another  
362 containing the powder for solution) was labelled only with the trade name. This introduced the  
363 possibility for misunderstanding, because the ampoule with the solution may be mistaken for the  
364 medicinal product containing the active substance and the patients may receive only water for  
365 injections. The product was relabelled to make it clear that the ampoule containing a solution  
366 contained water for injection, for use with the active substance. Treatments given by the intravenous  
367 (IV) route are associated with the highest rates of preparation and administration error due to issues  
368 such as incompatibility with diluents or by injecting bolus doses faster than the recommended slower  
369 infusion time. Medicinal products for IV use may be inadvertently given by the subcutaneous (SC),  
370 intradermal or intra-muscular (IM) route rather than by infusion. Cases of needle contamination can  
371 also result in accidental exposure to product or exposure to contaminated device (e.g. a case of  
372 adhesive arachnoiditis and paraplegia was reported when chlorhexidine, used as topical disinfectant in  
373 epidural or spinal anaesthesia procedures reached the meninges via a contaminated spinal/epidural  
374 needle).

375 A further source of error may be the use of medicinal products which have expired or been stored  
376 incorrectly (for example at the wrong temperature), which may lead to loss of efficacy.

377 Where medicinal products are self-administered by patients, the underlying reasons for medication  
378 error or accidental overdose may include lack of understanding of the dose regime. Risk factors for  
379 medication errors include decline in patients' renal or hepatic function (both associated with higher  
380 medication error rates), patients' impaired cognition, comorbidities, dependent living situation, non-  
381 adherence to medications, and polypharmacy. Advanced age is also a patient-related risk factor for  
382 medication errors.

383 Errors of omission (where the drug is not administered to the patient) may occur for a variety of  
384 reasons. Such errors can be critical if control of a medical condition requires regular medication (e.g. a  
385 patient with epilepsy was hospitalised with seizures when they ran out of supplies of carbamazepine  
386 and could not get a repeat or emergency supply). Other sources of errors of omission may include  
387 failure of communication between staff, especially when transferring patients between different units  
388 or hospitals, or failure to keep accurate drug administration records.

389 The use of multiple dose units to achieve a single dose (i.e. multiple vials of a drug or combinations of  
390 different tablet strengths) may be problematic if the number of dose units used is not closely  
391 monitored and recorded during administration. Patients may also not receive medication at the right  
392 time, e.g. on an empty stomach or in the morning rather than in the evening. Product information  
393 should include clear instructions on the most appropriate dosing time (if this is important) and whether  
394 the medicines can or should be taken with food and drink. There may also be use of medicinal  
395 products in patients who have allergies to such treatment; product information for all medicinal  
396 products should carry a contraindication for use in patients with known hypersensitivity to the active  
397 substance or excipients.

398 There is also the potential for errors in administration by visiting HCP and carers, who may be carrying  
399 multiple individual products for different patients in the same bag. Here, clear identifying features of a  
400 product can help to distinguish between products (e.g. ensuring that the presentation of a product,  
401 such as an insulin pen, differs to others of the same class so that they are less easily mixed up).  
402 Specific risk minimisation strategies e.g. for high strength and fixed combination insulin products

403 administered in pre-filled pens is provided in a guidance document included as an addendum to this  
404 guidance.

#### 405 *Device failure*

406 Device failure can occur in the post-marketing setting, e.g.:

- 407 • misplacement of dexamethasone intraocular implants has been reported and found to be due to  
408 mechanical failure of the implantation device; this led to introduction of training materials for the  
409 use of the device.
- 410 • breakage of levonorgestrel intrauterine devices on removal has been reported, meaning that pieces  
411 of the device have been left in situ.
- 412 • due to malfunction of the prefilled pen device several patients were reported to have missed a dose  
413 of adalimumab, one of whom was hospitalised with flare-up of the underlying disease.

414 A number of other examples of device-related medication errors are included in Annex 1. Where such  
415 failures are reported, MAHs should follow-up reports to obtain additional information as necessary and  
416 investigate whether the reports are substantiated, are isolated examples or are batch-wide and batch-  
417 specific. Further guidance on the elements of medication errors relating to defective medicines which  
418 should be reported or followed up for further details are included in the Good Practice Guide for the  
419 Recording, Coding, Reporting and Assessment of Medication Errors.

#### 420 **5.2.5.1. Reporting and Coding of medication errors**

421 Guidance on the reporting and coding of medication errors is provided in the Good Practice Guide for  
422 the Recording, Coding, Reporting and Assessment of Medication Errors.

#### 423 **5.2.5.2. Root cause analysis**

424 The root cause analysis (RCA) is a structured method used to analyse serious adverse events derived  
425 from errors. The goal is to identify both active errors (errors occurring at the point of the interface  
426 between humans and a complex system) and latent errors (the hidden problems within healthcare  
427 systems that contribute to the event).

428 A multidisciplinary team should analyse the sequence of events leading to the error. RCA should be  
429 performed at local level in order to prevent future harm by eliminating the latent errors and to ensure  
430 confidentiality.

431 A RCA should be conducted for any medication errors detected in the post-marketing environment so  
432 that lessons can be learned from serious incidents which may in turn reduce the likelihood of future  
433 incidents. The PSUR and RMP can both be used to document and analyse reports of medication error  
434 related to the design, presentation, labelling or naming of the medicinal product and where the need  
435 for risk minimisation measure and or communication can be taken..

436 A RCA has 3 basic steps:

- 437 1. Identification of the problem (including details of what happened, when, where and in what  
438 situation, and what the impact of the event is on stakeholders)
- 439 2. Identification of causes of the problem (describe the processes that led to the problem and identify  
440 the stages at which error could have or did occur)
- 441 3. Identification of solutions (identify possible or potential solutions from sources of error in the  
442 process)

## 443 **6. Measurement of success of measures taken**

### 444 **6.1. Risk minimisation measures**

445 Risk minimisation activities can mitigate the risk of medication error related to the medicinal product.

446 This guidance is complimentary to the recommendations in Good Vigilance Practice Modules V<sup>12</sup> (Risk  
447 management) and XVI<sup>13</sup> (Risk minimisation measures: selection of tools and effectiveness) which offer  
448 guidance on the development of risk minimisation tools.

#### 449 *Routine risk minimisation*

450 Routine risk minimisation measures apply to all products and include:

- 451 • the summary of product characteristics;
- 452 • the labelling;
- 453 • the package leaflet;
- 454 • the pack size(s);
- 455 • the legal status of the product.

456 Pack size limitations can reduce the risk of medication errors in the form of patients taking too many  
457 tablets (leading to overdose) and require the patient to return to the prescriber, who can check the  
458 status and progress of the patient and that the medicine is being used correctly.

459 It is important to consider whether critical information to avoid medication errors included in  
460 documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or  
461 care givers or whether more prominent warnings should be included on the packaging so that these  
462 are not overlooked (e.g. the labels for generic piperacillin/tazobactam carry a statement that they  
463 must not be mixed or co-administered with any aminoglycoside, and must not be reconstituted or  
464 diluted with lactated Ringer's (Hartmann's) solution; a similar warning is not required for the branded  
465 product as this has been reformulated to remove these incompatibilities).

#### 466 *Additional risk minimisation*

467 Additional risk minimisation measures may also be necessary in some circumstances and these  
468 encompass any measures beyond labelling, pack size and legal status. Additional risk minimisation  
469 measures should focus on the prevention of medication errors, but the burden of imposing such  
470 measures on patients, HCPs and the healthcare system should be balanced against the benefits.

471 The most common form of additional risk minimisation is educational materials for HCPs and patients,  
472 but other approaches may also be considered in agreement with National Competent Authorities (e.g.  
473 educational videos showing correct reconstitution and injection of a solution, prescriber's checklists to  
474 ensure that appropriate pre-treatment tests have been performed, demo-kits for complex devices).  
475 Educational materials are predominantly paper-based but as risk minimisation evolves it is likely that  
476 MAHs will consider supplementing such materials with by internet-based activities and new  
477 technologies in prescribing and dispensing systems to improve safe medication practice, such as smart  
478 phone apps, bar-coding and pill identifier websites. This should be discussed and agreed with national  
479 competent authorities in all cases with input sought from the Working Group on Quality Review of  
480 Documents as necessary.

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<sup>12</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129134.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf)

<sup>13</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/02/WC500162051.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf)

481 The development of additional risk minimisation materials should involve consultation with  
482 communication experts, patients and HCPs on the design and wording of educational material and that,  
483 where appropriate, it is piloted before implementation. Such measures may also be subject to  
484 additional pharmacovigilance to monitor their effectiveness.

### 485 **6.1.1. Error prevention at product design stage**

486 A number of common sources of medication error which should be considered at the product design  
487 stage are described in Annex 1 and include the appearance, size and shape of tablets, dilution  
488 problems with concentrated solutions and issues with the application and disposal of patches.  
489 Applicants should proactively consider all aspects of the design of the product, how it will be used and  
490 who will use it and conduct a suitable analysis of potential medication errors (see section 2.2.3). From  
491 these, the MAH should consider what risk minimisation may be introduced in the design of the product  
492 to reduce the risk of medication errors; a number of suggestions are included in Annex 2.

### 493 **6.1.2. Error prevention through naming, packaging and labelling (including** 494 **name review activities and use of colour)**

495 Look alike and sound alike names of medicinal products which could pose a risk to patients' safety  
496 should be avoided. The name of a medicinal product could be an invented name not liable to confusion  
497 with a common name (e.g. INN) or a common name or scientific name accompanied by trade mark or  
498 name of the MAH.

#### 499 **6.1.2.1. Naming**

##### 500 *International Non-proprietary Name (INN)*

501 The World Health Organisation (WHO) has issued guidance on devising new International  
502 Nonproprietary Names (INN) to facilitate the identification of pharmaceutical substances or active  
503 pharmaceutical ingredients, including the following recommendations:

- 504 • INN should be distinctive in sound and spelling. They should not be inconveniently long and not be  
505 liable to confusion with names in common use.
- 506 • Use of common 'stems' for products which are in related pharmaceutical classes (e.g. -azepam for  
507 diazepam derivatives, -bactam for beta-lactamase inhibitors, gli- for sulfonamide hypoglycaemics).
- 508 • To avoid confusion neither trade-marks nor product brand names should be derived from INNs nor  
509 contain common stems used in INNs.
- 510 • It is important to note that the alternating use of brand names and INNs may lead to inadvertent  
511 overdosing, should patients be treated with multiple products containing the same active  
512 substance.

513 However, it is also important to consider the potential for confusion between products due to  
514 similarities in the INN. These can arise from phonetic (sound-alike), orthographic (look-alike) and  
515 cognitive errors. There have been instances where products with similar INNs have been inadvertently  
516 used (e.g. flucloxacillin recorded in place of the prescribed fluvoxamine, prochlorperazine prepared  
517 instead of promethazine). The FDA and ISMP recommend the use of Tall Man letters where part of the  
518 INN or drug name is written in upper case, to help distinguish sound-alike and look-alike INN or drug  
519 names from one another, making them less prone to mix-ups (e.g. NovoLOG and NovoLIN and  
520 HumaLOG and HumuLIN<sup>14</sup>).

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<sup>14</sup> <http://www.ismp.org/tools/confuseddrugnames.pdf>



521 *Brand Name*

522 The CHMP has issued guidance on the acceptability of names for human medicinal products processed  
523 through the centralised procedure<sup>15</sup>. This includes that the name should not convey a promotional  
524 message, have 'bad' connotations in any of the official languages, be misleading in therapeutic,  
525 pharmaceutical or composition terms or cause confusion in print with any other branded product or  
526 established INN. The MAH should take this guidance into account when proposing invented names to  
527 the competent authorities.

528 There have been some examples of brand name mix-ups or errors, e.g.:

- 529 • In Italy, Diamox (acetazolamide) has been mistaken for Zimox (amoxicillina triidrato)
- 530 • In Ireland, confusion arose between the brand names Lasix (frusemide) and Losec (omeprazole)  
531 which may look similar when handwritten. There have been cases of product name confusion  
532 between Plavix (clopidogrel) and Pradaxa (dabigatran etexilate), particularly as both products have  
533 a 75mg dosage form and daily posology
- 534 • There has been confusion between the trade names Faustan (active substance diazepam) and  
535 Favistan (active substance thiamazole) and consequently the MAH changed the name of the  
536 diazepam medicinal product to Diazepam Temmler to reduce the risk of medication error due to  
537 mix-ups between the two medicinal products.

538 For centrally authorised medicines, the potential for medication errors arising from the name of the  
539 medicinal product is assessed (for centrally authorised medicinal products) by the EMA's Name Review  
540 Group, who have issued guidance on this matter<sup>16</sup>. The Group reviews the proposed (invented) name  
541 of medicinal products and considers whether invented names may convey misleading therapeutic or  
542 pharmaceutical connotations, be misleading with respect to product composition of the product, be  
543 promotional, cause confusion in identifying medicinal products, or create difficulties in pronunciation  
544 (or have any inappropriate connotations) in the different EU official languages.

#### 545 **6.1.2.2. Labelling and livery**

546 The aim of good labelling is: correct description of the medicine, clear product selection and  
547 identification, information ensuring safe storage, selection, preparation, dispensing, and administration  
548 as well as track and trace. The design of labelling and packaging may lead to mis-selection of medicinal  
549 products, therefore all medicinal products placed on the market are required by Community law to be  
550 accompanied by labelling and package leaflet which provide a set of comprehensible information  
551 enabling the use safely and appropriate. Articles 54–57 and 61-63 of Directive 2001/83/EC specify the  
552 information which must appear on the outer packaging (or immediate packaging where there is no  
553 outer packaging), including: the name of the medicinal product, dosage unit, pharmaceutical form, list  
554 of excipients, method/rout of administration, warning that the products should be kept out of the sight  
555 and reach of children, expiry date, batch number, contents by weight, by volume or by unit  
556 requirements, special storage or disposal conditions, information on Braille. On the printed outer  
557 packaging material, an empty space should be provided for attaching the prescribed dose. The use of  
558 the Quality review of Documents (QRD) template ensures that the product is labelled with this  
559 minimum information and this can help to clearly identify the product and reduce the risk of confusion  
560 with other products. The readability guideline<sup>17</sup> provides guidance to ensure that the information

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<sup>15</sup>

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2014/06/WC500167844.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167844.pdf)

<sup>16</sup>

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2014/06/WC500167844.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167844.pdf)

<sup>17</sup> [http://ec.europa.eu/health/files/eudralex/vol-2/c/2009\\_01\\_12\\_readability\\_guideline\\_final\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf)

561 presented is accessible and understandable. In addition, several organisations have published design  
562 for safety guidances (NHS). The special space constraints on small containers (vial) and blister packs  
563 should also be taken into consideration.

564 *Products with the same manufacturer*

565 MAHs may adopt packaging and labelling which supports a common “trade dress” and this can serve as  
566 an identifying mark and to create visual associations between multiple products from the same  
567 manufacturer. However, this assumes perfect performance by both healthcare professionals and  
568 patients and it is therefore important to assess such livery to determine whether it may give rise to a  
569 risk of medication error. Package design and livery should not compromise other distinguishing  
570 features of the medicinal product e.g.:

- 571 • a case of unintended pregnancy was reported when a product used to treat symptoms of  
572 menopause was dispensed in error as oral contraception due to similarities in the packaging livery  
573 and a similar combination of ingredients as other oral contraceptives.
- 574 • Patients were mistakenly vaccinated with Repevax instead of Revaxis due to similarity in names,  
575 labelling and packaging; children over 10 years of age and unvaccinated children did not receive  
576 the appropriate booster immunisation against diphtheria, tetanus and poliomyelitis with Revaxis.  
577 The MAH amended the packaging for Repevax to help distinguish it more clearly from Revaxis and  
578 this change was also communicated to HCPs.

579 If a MAH markets two or more products in the same therapeutic area which have a similar company  
580 livery, the possibility of mix-ups between the medicinal products must be considered (and labelling  
581 amended accordingly). This issue has been identified for injectable insulin products;

- 582 • a patient developed hypoglycaemia after being prescribed Insulin Novorapid 16 units twice daily  
583 instead of Novomix
- 584 • the presentation of different insulins in the same Flexpen device has led to reports of mix-up  
585 between these two insulins.

586 Clear distinction between medicinal products may be achieved by use of different colours, if such  
587 colours can be clearly distinguished from one another by the majority of users. However, this must  
588 take into account that red-green colour vision deficiencies affects up to 1 in 12 men and 1 in 200  
589 women. The ISMP have issued guidance<sup>18</sup> which highlights the potential uses of colour e.g.

- 590 • colour coding, where there is a standard application of colour to aid in classification and  
591 identification;
- 592 • colour differentiation, which makes certain features stand out, or helps to distinguish one item  
593 from another;
- 594 • colour matching, where colour is used to guide matching up of various components of multi-  
595 part medicinal products.

596 The guidance highlights the problems which may arise from these, including a limited variety of  
597 available colours and lack of common understanding of colour coding conventions.

598 Specific risk minimisation strategies e.g. for high strength and fixed combination insulin products  
599 administered in pre-filled pens are provided in a guidance document included as an addendum to this  
600 guidance.

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<sup>18</sup> <http://www.ismp.org/newsletters/acutecare/articles/20031113.asp>

601 There may be other key data elements which are important to emphasize visually on the outer  
602 packaging and on the medicinal product itself, to prevent mix-ups. For products available in different  
603 strengths, and where the risk of under- or over-dose is potentially severe, it may be necessary to  
604 highlight the strength by use of increased font size and a warning colour such as red (noting the  
605 provisions for those with red-green colour blindness). Other measures may include the use of a  
606 'hatching' effect to differentiate one similar product from another, or the introduction of a 'warning  
607 label' to draw attention to critical information (e.g. "CAUTION HIGH STRENGTH").

#### 608 *Products with different manufacturers*

609 In addition to the review of names and packaging, applicants should consider the appearance and  
610 name of their medicinal product in comparison to medicinal products from other manufacturers used in  
611 similar indications, and the potential for confusion between medicinal products. This is particularly  
612 relevant for vaccines which are generally stored together in refrigerators in the local surgery and  
613 where the potential exists for accidentally selecting the wrong product due to similarities in appearance  
614 between medicinal products, and is also relevant for medicinal products which may be stored in the  
615 patient's fridge at home, such as injectable insulin products made by different manufacturers.

616 Different manufacturers make use of colour as part of their brand and livery and in most cases there is  
617 no set colour scheme that must be used for a given indication or class of medicinal products (although  
618 there are isolated examples; in the UK there is a colour-coding convention for warfarin tablets wherein  
619 0.5 mg tablets are white, 1 mg tablets are brown, 3 mg tablets are blue and 5 mg tablets are pink).  
620 However, choice of colour should be considered in product design (e.g. pharmacists have raised  
621 concerns that a fixed-dose combination of vilanterol and fluticasone furoate with indications in the  
622 maintenance treatment of asthma and COPD) may be used in error for the relief of symptoms of  
623 asthma due its presentation in an inhaler device with blue parts, blue being a common choice of colour  
624 for reliever inhalers in some EU Member States).

#### 625 **6.1.2.3. Use of illustrations and pictures in product information**

626 Product information often includes illustrations on use of the product or reconstitution prior to use. The  
627 MAH should consider on a case-by-case basis whether it is clearer to use photographs or  
628 diagrams/pictograms to illustrate correct use of a product within product information. Any descriptions  
629 which accompany pictures should describe clearly only what is shown in the picture. As mentioned in  
630 section 2.2.3, human factor testing can be very useful in demonstrating that instructions for use can  
631 be understood and followed without error.

632 Non-prescription medicinal products are likely to be used without the supervision of a HCP and labelling  
633 and should therefore include all relevant information for the lay reader about safe use of the medicinal  
634 product. This includes use of diagrams and pictograms and advice on seeking medical help if there are  
635 any concerns.

636 The QRD recommendations on pack design and labelling for centralised non-prescription products<sup>19</sup>  
637 summarises basic principles.

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[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2011/04/WC500104662.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/04/WC500104662.pdf)

### 638 **6.1.3. Risk minimisation tools and activities**

#### 639 **6.1.3.1. For patients/caregivers**

640 Key to risk minimisation and prevention of medication errors is the provision of a suitable PL which  
641 describes the correct use of the medicinal product. There is a requirement to include a user-tested PL  
642 in the packaging of the medicinal product in most cases. However, it is important that large-print and  
643 Braille leaflets are also made available, particularly for patients with sight problems. There is increasing  
644 use of the internet to provide information concerning medicinal products, for example, training  
645 materials for the insertion of etonogestrel contraceptive implants are provided on the MAH's website to  
646 complement formal training and are intended to minimise the risk of medication error through  
647 incorrect insertion. Additionally, National Competent Authorities may publish guidance on their  
648 websites on practices to reduce the risk of medication error (e.g. the Medicines and Healthcare  
649 products Regulatory Agency in the UK included an article in its 'Drug safety Update' bulletin  
650 highlighting that insulin degludec was available in additional higher strength than existing insulins and  
651 that care was needed to minimise risk of error, including training for patients<sup>20</sup>).

652 Participants in the EMA workshop on medication errors (2013) suggested a number of activities to  
653 mitigate the risk of medication error, which are not part of any formal guidance. These include the use  
654 of separate medicine cabinets for different household members and the use of more sophisticated tools  
655 that can help to prevent medication errors (e.g. smart phone applications which remind patients to  
656 take their medications on time and track medications which have been taken, and websites which carry  
657 pill identifier tools to help patients identify medicines).

#### 658 **6.1.3.2. For Healthcare professionals**

659 HCPs are responsible for ensuring that patients are prescribed and receive the appropriate medication  
660 without errors. Where patients are responsible for the administration of the medication themselves,  
661 HCPs should ensure that the patient understands how to self-administer the medications appropriately  
662 in order to minimise the risk of medication errors.

##### 663 *Prescribers*

664 Prescribers have an important role in determining that the treatment is appropriate for the patient,  
665 based on the licensed indication as described in the product information. The use of pop-up reminders  
666 in e-prescribing systems may be useful in reminding the prescriber to specify details of the  
667 prescription, e.g. strength of insulin. Other tools which may assist HCPs in prescribing appropriately  
668 may include the use of reminder cards (e.g. the healthcare professional's reminder card for  
669 vismodegib, which is teratogenic, contains information for men and women on the importance of  
670 adequate contraception and pregnancy testing), reminder posters and prescriber guides and checklists.

##### 671 *Pharmacists*

672 Pharmacists may play an important role in verifying that the treatment is appropriate for the patient  
673 and identifying potential prescribing errors before the medication is dispensed to the patient. The  
674 pharmacist may identify issues by speaking to the patient or by consulting dispensing records.  
675 Although it is important to be discreet and not to undermine the confidence of the patients in the  
676 prescriber, the pharmacist is well-placed to ask such questions as whether the patient has received the  
677 medicine before. If any aspect of the prescription appears to be inappropriate for the patient (e.g. it is  
678 contraindicated, dosage appears to be excessive, or if a medicine requires a negative pregnancy test

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<sup>20</sup> <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266132>

679 before being dispensed) this can usually be verified by contacting the prescribers whose details are  
680 included on the prescription.

681 Pharmacists are also well placed to counsel patients at the point of dispensing on the use of their  
682 medications, including dose regimen, timing of medicine intake in relation to other medicines or food  
683 and use of devices such as inhalers, and to answer any questions from patients.

684 The following list of common dispensing errors identified in hospital Pharmacies<sup>21</sup> highlights the  
685 importance of checking that details of each prescription have been transcribed correctly and medicinal  
686 products selected carefully in order to minimise the risk of medication error, including:

- 687 • *Dispensing medicinal product for the wrong patient (or for the wrong ward)*
- 688 • *Dispensing the wrong medicinal product*
- 689 • *Dispensing the wrong drug strength*
- 690 • *Dispensing at the wrong time*
- 691 • *Dispensing the wrong quantity*
- 692 • *Dispensing the wrong dosage form*
- 693 • *Dispensing an expired or almost expired medicinal product*
- 694 • *Omission (i.e. failure to dispense)*
- 695 • *Dispensing a medicinal product of inferior quality (pharmaceutical companies)*
- 696 • *Dispensing an incorrectly compounded medicinal product (compounding in pharmacy)*
- 697 • *Dispensing with the wrong information on the label:*
  - 698 ○ *Incorrect patient name*
  - 699 ○ *Incorrect medicinal product name*
  - 700 ○ *Incorrect strength*
  - 701 ○ *Incorrect instruction (including incorrect dosage)*
  - 702 ○ *Incorrect medicinal product quantity*
  - 703 ○ *Incorrect dosage form*
  - 704 ○ *Incorrect expiry date*
  - 705 ○ *Omission of additional warning(s)*
  - 706 ○ *Incorrect pharmacy address*
  - 707 ○ *Other labelling errors*
- 708 • *Dispensing with the wrong verbal information to the patient or representative*

709 For some of these errors, the risk may be increased for some medications. These include medications  
710 with similar names (INN or brand name) or similar packaging, medicinal products which are available  
711 in multiple strengths and or formulations, including different delivery devices, and situations where the  
712 same active ingredient is present in different medicinal products for different indications.

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<sup>21</sup> Br J Clin Pharmacol. Jun 2009; 67(6): 676–680.

#### 713 **6.1.4. New technologies**

714 A study of the prevalence and causes of prescribing errors in general practice in England<sup>22</sup> suggested  
715 that prescribing or monitoring errors were detected for one in eight patients. The most common types  
716 of prescribing error were “incomplete information” (37.9%) “unnecessary drug” (23.5%),  
717 “dose/strength error” (14.4%) and “omission” (11.8%). The study recommended GP training,  
718 continuing professional development, clinical governance, the effective use of clinical computers, and  
719 improving systems to support safe medicines management.

720 In recent years there has already been increased use of technology in prescribing and dispensing  
721 systems. Such new technologies go beyond the regulatory tools for mitigating the risk of medication  
722 error (which are the responsibility of national competent authorities and MAHs) but they may provide a  
723 valuable contribution to minimising the risk of medication errors. The inclusion of the following in this  
724 guidance is intended only to raise awareness of those tools, including:

- 725 • Use of prescribing software for general practitioners including prescribing decision support software  
726 which can check the correct medicinal product and dosage form, correct dose calculations, cross-  
727 check information on allergies, provide information on known drug interactions and adjustment of  
728 dosages in patients with renal or hepatic dysfunction;
- 729 • Electronic prescribing services (EPS) where prescriptions are sent electronically to a dispenser  
730 (such as a pharmacy) of the patient's choice
- 731 • Automated medicine-dispensing robots and automated dispensing cabinets in hospitals, which can  
732 reduce dispensing errors by packaging, dispensing, and recognizing medicinal products using bar  
733 codes
- 734 • Use of bar-coded medication administration (BCMA) systems in hospitals to check and record that  
735 the right patients has received the right medicinal product at the right time; such systems can be  
736 expensive to implement and maintain but were shown to reduce the medication error rate in an  
737 intensive care unit by 56%
- 738 • Use of electronic health record (EHR) to ensure that all relevant information is taken into  
739 consideration at prescription and during administration.

#### 740 **6.1.5. Criteria to assess effectiveness of error prevention during post-** 741 **marketing**

742 The difficulties around standardised coding for medication errors in spontaneous reporting systems  
743 means that such systems are unlikely to be able to collect all incidents of medication error and will not  
744 collect reports of ‘near misses’. There are a number of International Classification of Diseases (ICD)  
745 codes which relate to medication errors and which may be useful in the collection of data in this area.

746 Collaboration between different national reporting systems which collect data on medication errors,  
747 regardless of whether or not they were associated with clinical consequences, are an important source  
748 of both process and outcome data but for medication errors associated with ADR the exchange of  
749 information is a legal requirement. Article 107a(5) of Directive 2001/83/EC states that the EU Member  
750 States shall ensure that reports of suspected adverse reactions arising from an error associated with  
751 the use of a medicinal product that are brought to their attention are made available to the  
752 Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible  
753 for patient safety within that EU Member State. They shall also ensure that the authorities responsible

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<sup>22</sup> [http://www.gmc-uk.org/Investigating\\_the\\_prevalence\\_and\\_causes\\_of\\_prescribing\\_errors\\_in\\_general\\_practice\\_\\_\\_The\\_PRACTiCe\\_study\\_Repo\\_rpt\\_May\\_2012\\_48605085.pdf](http://www.gmc-uk.org/Investigating_the_prevalence_and_causes_of_prescribing_errors_in_general_practice___The_PRACTiCe_study_Repo_rpt_May_2012_48605085.pdf)

754 for medicinal products within that EU Member State are informed of any suspected adverse reactions  
755 brought to the attention of any other authority within that Member State. These reports shall be  
756 appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.  
757 Reporting requirements for MAHs and national competent authorities for medication errors without  
758 ADR are addressed in the Good Practice Guide for the Recording, Coding, Reporting and Assessment of  
759 Medication Errors.

760 Routine pharmacovigilance through monitoring of spontaneous reporting systems is the most  
761 commonly-employed method of measuring the success of risk minimisation activities but it has major  
762 limitations and alternative proposals should be made wherever possible.

763 A Post-Authorisation safety Study (PASS) can be a useful method to show how patterns of use or  
764 reporting of errors may have changed before and after safety communications or changes in product  
765 labelling, and may also identify sources of medication in the post-approval setting, e.g.:

- 766 • For aflibercept, the potential risk of medication errors due to overdose from the pre-filled syringe is  
767 being addressed by an observational PASS to evaluate physician and patient knowledge of safety  
768 and safe use information of aflibercept in Europe.
- 769 • Medication errors due to the incorrect application of rivastigmine patches were addressed by  
770 circulation of a DHPC but spontaneous reporting showed cases were still being reported with no  
771 clear trends of improvement observed after the issuance of the DHPC. The MAH was asked to  
772 implement further risk minimisation measures to manage the risk of medication error through  
773 overdose including updates to product information and educational material for prescribers. The  
774 MAH was required to measure the success of these measures through additional Pharmacovigilance  
775 in the form of a DUS.

776 Another commonly employed method to measure the outcome of risk minimisation activities is a  
777 survey or questionnaire used to ascertain the retention and implementation of key risk minimisation  
778 messages by HCPs and/or patients, e.g.

- 779 • For insulin lispro, the risk of medication errors potentially arising due to confusion with different  
780 presentations with different strengths is being targeted through dissemination of a DHPC and  
781 patient communication materials. A patients and physician survey is underway to assess the  
782 effectiveness of the DHPC.
- 783 • For cabazitaxel, the risk of medication errors related to errors in reconstitution of the product led  
784 to dissemination of a DHPC and updates to product information in order to improve the readability  
785 of the information for reconstitution. The effectiveness of the DHPC is being conducted through a  
786 survey of hospital Pharmacists.

787 Survey approaches can be highly susceptible to recall bias on the part of the interviewees and  
788 therefore such studies require careful design. Further guidance on the selection of risk minimisation  
789 tools and the measurement of the outcomes of these measures is provided in GVP Module XVI, 'Risk  
790 minimisation measures: selection of tools and effectiveness indicators'<sup>23</sup>; Guidance on the key  
791 elements of survey methodology is included as an Appendix to GVP Module XVI.

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<sup>23</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/02/WC500162051.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf)

## 792 **6.2. Specific considerations in high risk groups**

### 793 **6.2.1. Paediatric patients**

794 Paediatric patients may be at particularly high risk of medication errors due to their variation in age,  
795 size and weight, body surface area (BSA) and degree of development. This is reflected in the dosing  
796 instructions for some paediatric products which express dosage and strength by bodyweight rather  
797 than by age in months or years.

798 Overdose was the most commonly reported medication error (accounting for 21% of all reports) in a  
799 study of paediatric patients (Manias et al 2013<sup>24</sup>) while underdosing in certain paediatric specialties  
800 was the most commonly reported medication error in these settings (Bolt et al 2014<sup>25</sup>). These  
801 conflicting findings indicate a more general risk of dosing errors (leading to either over- or  
802 underdosing) in paediatric patients. Paediatric prescribing is often determined by the patient's weight,  
803 yet weight is not measured before each prescription and can change over time meaning that  
804 recalculation of drug doses is required. Due to the need to find the right dose based on weight (or  
805 BSA) for the majority of paediatric medicines, mathematical miscalculations may be more likely in  
806 paediatric patients than adults.

807 Occasionally there is a need for complex dilutions by medics/nurses/pharmacists; medication errors  
808 with infusion of fluids and electrolytes are common. For liquid oral medications there is some evidence  
809 that oral syringes may be the most accurate dosing device<sup>26</sup>. However, liquid formulations may present  
810 a risk of medication error if the wrong dosing device is used to deliver them (e.g. a liquid oral  
811 formulation of paracetamol was presented with a dropper graduated in mL for infants less than 3 years  
812 and an oral syringe graduated in mL for infants older than 3 years; use of the oral syringe in infants  
813 could lead to a risk of overdose).

814 Historically there has been a lack of development of paediatric medicines and lack of clear guidance on  
815 paediatric dosing in product information or other sources, leading to off-label use of medicinal products  
816 with indications in adult populations. The situation has improved with the introduction of the paediatric  
817 regulation in 2006 (Regulation (EC) No 1901/2006) that places some obligations for the applicant  
818 when developing a new medicinal product, in order to ensure that medicines to treat children are  
819 appropriately authorised for use in children, and to improve collection of information on the use of  
820 medicines in the various subsets of the paediatric population. However, the ongoing limited availability  
821 of paediatric formulations may lead to misuse of product formulated for adults.

822 The EMA workshop on medication errors noted that the risk of medication errors is particularly high in  
823 specific paediatric groups such as neonates, where age-specific dosing requirements are based on the  
824 known influence of ontogeny on the disposition of drugs. The weight of neonates may change rapidly  
825 over a short period of time, making the appropriate dose adjustment critical. Differences in the  
826 pharmacokinetic (PK) profile of neonates compared to that of older children probably contribute  
827 significantly to them being at higher risk of overdose and being less able to tolerate a medication error  
828 than older patients. This is largely due to their still-developing hepatic enzyme systems and renal  
829 systems, both vital for metabolism and clearance, as well as the variable absorption, delayed gastric  
830 emptying and reduced gut motility in neonates.

831 Apart from neonates, the risk of medication errors in paediatric patients may also be increased in  
832 circumstances where high risk medicines, specific drug combinations and formulations are used, or

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<sup>24</sup> Medication errors in hospitalised children. Elizabeth Manias, Sharon Kinney, Noel Cranswick, Allison Williams  
Journal of Paediatrics and Child Health. 01/2014; 50(1):71-7

<sup>25</sup> Bolt R et al, Journal of Clinical Pharmacy and Therapeutics, 2014, 39, 78–83

<sup>26</sup> Padden Elliott J et al, Influence of Viscosity and Consumer Use on Accuracy of Oral Medication Dosing Devices  
Journal of Pharmacy Technology, August 2014; vol. 30, 4: pp. 111-117



833 where untrained healthcare workers are involved, and in transitions of care such as admission and  
834 discharge. Paediatric patients with chronic conditions and/or complex medication regimes (e.g. children  
835 with learning difficulties, oncology patients) may also be at particular risk of medication error due to  
836 the added complexities of dosing or polypharmacy in these patients.

837 Consideration should also be given to the prevention of accidental ingestion or other unintended use of  
838 medicinal products by children. A standard statement that medicinal products should be kept out of the  
839 sight and reach of all children is included on the labelling for all medicinal products and in practice the  
840 use of locked containers or medicine cabinets which cannot be reached by children should be  
841 encouraged.

### 842 **6.2.2. Elderly patients**

843 The elderly account for 34% of all written prescriptions and are at high risk of medication errors.  
844 Elderly patients frequently use multiple medicinal products (polypharmacy) and this can lead to mix-  
845 ups and other administration errors. Elderly patients may also have difficulty swallowing, particularly  
846 in diseases such as stroke or Parkinson's disease. This can lead to accidental underdosing, which  
847 should be managed appropriately by use of formulations which are easier for such patients to swallow.  
848 Other problems which are common in elderly patients and which may increase the risk of medication  
849 error include insufficient intake of fluids. There may also be excessive use of over-the-counter (OTC)  
850 products, e.g. laxatives or herbal medicinal products, which doctors are likely to be unaware of but  
851 pharmacists may be better able establish. Older patients with diabetes may be more likely to have  
852 impaired eye sight than younger patients which may have implications for the correct use of insulin  
853 pens.

854 Elderly patients, particularly those in shared living environments with caregivers who have  
855 responsibility for several patients, may be vulnerable to mix-ups with other patients' medications.  
856 Older patients with manual dexterity issues may also have difficulties opening containers or blisters or  
857 in handling medical devices and this should be taken into consideration in product design for medicinal  
858 products intended for diseases of old age.

859 It is important the appropriate materials for elderly patients are developed and user-tested, including  
860 use of large print text and Braille for patients with impaired eye sight it is also important not to rely  
861 solely on the provision of information via the internet, as elderly patients are less likely to make use of  
862 such materials than younger patients. For (very) elderly patients, the internet is the least preferred  
863 option for provision of educational materials to ensure correct use of a medicinal product. For this age  
864 group, the caregiver, nurse and family should play an important role for the correct use of the  
865 medicinal product and should be involved pro-actively by the doctor or pharmacist. It is vital that  
866 elderly patients are asked explicitly what they want and how they feel about a prescribed medicinal  
867 product, rather than imposing a medication without considering the patient's circumstances and ability  
868 to use it safely.

### 869 **6.2.3. Patients with visual impairment or low literacy**

870 GVP Module V (Risk Management Systems) highlights that when a medicinal product is likely to be  
871 used by a visually impaired population, special consideration should be given to the potential for  
872 medication error. Where appropriate, medication error should be included as a safety concern and  
873 appropriate risk minimisation measures proposed to address the possibility of medication error due to  
874 visual impairment. Patients with low literacy are likely to have difficulty following and understanding  
875 instructions for use. This may be a sensitive issue to discuss with patients or their carers and  
876 underlines the importance of patients being fully counselled on the use of their medicine by HCPs in  
877 preference to being left to educate themselves using printed materials.

## 878 **6.3. Communication**

### 879 **6.3.1. General principles of good communication in relation to medicines** 880 **information**

881 For communication of safety information in product information, the CHMP has issued guidance on the  
882 readability of the labelling and package leaflet of medicinal products for human use<sup>27</sup>. The standard  
883 content and format of the PL is defined in Directive 2001/83/EC and it should be written in simple  
884 language, understandable by the layperson. The PL must be up-to-date and reflect all relevant  
885 information from the SmPC and be user-tested to show that users can find and understand  
886 information. The level of risk should be communicated clearly and listed adverse reactions side-effects  
887 should be assigned an appropriate frequency category. The use of the term “unknown” or “not known”  
888 in relation to frequencies of ADRs should be avoided whenever possible in the PL as this is not helpful  
889 to patients in helping them to understand the degree of risk, and may even raise alarm). It would be  
890 better to use language such as “Other side effects which may occur include...” or “Although it is not  
891 know exactly how often it occurs...” (or similar) in situations where no frequency has been designated  
892 for a given ADR.

893 In 2003, the Committee of Experts on Pharmaceutical Questions created the Expert Group on Safe  
894 Medication Practices to review medication safety and to prepare recommendations to specifically  
895 prevent adverse events caused by medication errors in European health care. The Expert Group<sup>28</sup> has  
896 made a number of recommendations about communicating medicines information to patients. Key to  
897 these recommendations is the need to ensure that patient information and format is tailored to those  
898 who will receive it and their health literacy levels, not only to adult “standard” consumers. Large-print  
899 versions of the PL should be made available on request for partially-sighted people while formats  
900 perceptible by hearing should be provided for blind people (although Braille may be appropriate in  
901 some cases). The Expert Group also made recommendations on the importance of patient counselling  
902 (as the PL can be lengthy and is often not read).

903 It is also important to consider communication on medicines safety for HCPs. This is largely based on  
904 information presented in the SmPC, but these documents can be lengthy and they are not always  
905 consulted. When the risk for Medication error has been identified and the need for additional  
906 communication tools has been identified, educational materials and/or Direct Healthcare Professional  
907 communications (DHPC) may highlight key safety information which is important for the prescriber or  
908 treating HCPs to be aware of. However, these materials must reach the appropriate users and full use  
909 must be made of these materials in order to minimise risk. It is important that a comprehensive  
910 communication plan is agreed between MAHs and competent authorities for dissemination of such  
911 materials. In some circumstances it may be more efficient to disseminate information through  
912 professional bodies rather than directly to HCPs and this should be considered as an option. The  
913 effectiveness of these additional measures should be captured and analysed in the PSURs and RMPs.

914 At a European level, the SCOPE project has a dedicated work package<sup>29</sup> which is focussing on risk  
915 communications about medicines. Information will be collected on risk communications practice in the  
916 EU network to understand the communication channels and tools used, with frequency, strategy, and  
917 engagement approaches. A study will also be conducted on the knowledge, attitudes and preferences  
918 of target audiences towards different communications tools and channels in Member States to  
919 determine the effectiveness of different risk-communication methods. This will be used to develop a  
920 series of recommendations in the form of a communications toolbox including guidance for the media

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<sup>27</sup> [http://ec.europa.eu/health/files/eudralex/vol-2/c/2009\\_01\\_12\\_readability\\_guideline\\_final\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf)

<sup>28</sup> Creation of a better medication safety culture in Europe: Building up safe medication practices', Council of Europe Expert Group on Safe Medication Practices (2006)

<sup>29</sup> <http://www.scopejointaction.eu/work-packages/wp6-risk-communications/>

921 on scientific risk communication. There will be a particular focus on web portals and development of  
922 guidance (informed by the above activities) on the preparation of information for web portals,  
923 successful presentation and coordination of information on these platforms in the EU network. Delivery  
924 of the toolbox to EU Member States will be supported by training.

## 925 **7. Operation of the EU regulatory network**

926 As described in GVP Module VI on management and reporting of adverse reactions to medicinal  
927 products, reports of medication errors associated with harm are subject to the normal reporting rules  
928 as for individual case safety reports (ICRSs).

929 Medication errors not associated with harm should be discussed in the PSUR and notified as an  
930 emerging safety issue if there is an impact on the benefit-risk balance of the product. Detailed  
931 guidance on the reporting requirements for medication error and intercepted errors (or near misses) is  
932 provided in the Good Practice Guide for the Recording, Coding, Reporting and Assessment of  
933 Medication Errors.

### 934 **7.1. Competent authorities in Member States**

935 Article 107a of Directive 2001/83/EC imposes a legal obligation on EU Member States to record and  
936 report suspected adverse reactions that occur in its territory which are brought to its attention from  
937 healthcare professionals and patients. For this purpose EU Member States operate a pharmacovigilance  
938 system to collect information on the risks of medicinal products with regard to patients' or public  
939 health, including suspected adverse reactions arising from use of the medicinal product within the  
940 terms of the marketing authorisation as well as from use outside the terms of the marketing  
941 authorisation, and to adverse reactions associated with occupational exposure [Directive 2001/83/EC,  
942 Article 101(1)]. This includes suspected adverse reactions arising from errors with human medicinal  
943 products.

944 EU Member States should also take all appropriate measures to encourage patients, doctors,  
945 pharmacists and other healthcare professionals to report suspected adverse reactions, including those  
946 arising from medication errors, to the national competent authority (Directive 2001/83/EC, Article  
947 102). For this purpose patient reporting should be facilitated through the provision of alternative  
948 reporting formats (i.e. through various media) in addition to web-based formats which Competent  
949 Authorities provide on their national websites.

950 It is particularly important that awareness of this reporting mechanism is raised amongst patients at a  
951 national level and national competent authorities should work with National patient safety  
952 organisations (PSO) to facilitate this. There are a number of critical factors essential to stimulate the  
953 reporting from patients, including clarity about what to report and how, including a feedback  
954 mechanism to encourage further engagement.

955 Article 107a(5) of Directive 2001/83/EC outlines the key responsibilities of national competent  
956 authorities in relation to the reporting of ADRs associated with medication error:

957 *Member States shall ensure that reports of suspected adverse reactions arising from an error*  
958 *associated with the use of a medicinal product that are brought to their attention are made available to*  
959 *the Eudravigilance database and to any authorities, bodies, organisations and/or institutions,*  
960 *responsible for patient safety within that Member State. They shall also ensure that the authorities*  
961 *responsible for medicinal products within that Member State are informed of any suspected adverse*  
962 *reactions brought to the attention of any other authority within that Member State. These reports shall*  
963 *be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.*

964 Furthermore, EU Member States have the obligation to evaluate the information held in their  
965 pharmacovigilance system scientifically, to detect any change to a medicine's risk-benefit balance, to  
966 consider options for risk minimisation and prevention and to take regulatory action concerning the  
967 marketing authorisation as necessary. The general responsibilities of competent authorities in relation  
968 to risk management are outlined in GVP module V and apply likewise to the management of medication  
969 errors.

## 970 **7.2. Pharmacovigilance Risk Assessment Committee (PRAC)**

971 Article 61a (6) of Regulation (EC) No 726/2004 outlines the mandate of the Pharmacovigilance Risk  
972 Assessment Committee (PRAC) which shall cover all aspects of the risk management of the use of  
973 medicinal products for human use including the detection, assessment, minimisation and  
974 communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of  
975 the medicinal product for human use, the design and evaluation of post- authorisation safety studies  
976 and pharmacovigilance audit.

977 The PRAC shall be responsible for providing recommendations to the Committee for Medicinal Products  
978 for Human Use and the coordination group on any question relating to pharmacovigilance activities in  
979 respect of medicinal products for human use and on risk management systems and it shall be  
980 responsible for monitoring the effectiveness of those risk management systems (Article 56 (1)(aa) of  
981 Regulation (EC) No 726/2004).

982 This includes any risk minimisation measures to prevent or minimise the risk of medication errors,  
983 including the assessment of their effectiveness in line with the provisions of GVP module XVI.

## 984 **7.3. Patients and healthcare professionals**

985 The EMA workshop on medication errors called for pro-active engagement and capacity building with  
986 patient consumer groups and healthcare professionals on a systematic basis to improve safe  
987 medication practices. To ensure risk minimisation measures tailored to prevent or minimise medication  
988 errors are effective in practice, patients, healthcare professionals but also caregivers and other  
989 healthcare providers depending on the healthcare delivery system where the medicinal product is  
990 intended to be used, should be included systematically in the design, user testing and communication  
991 strategy of risk minimisation measures.

## 992 **7.4. Marketing authorisation applicant or holder**

993 MAHs are required to operate a pharmacovigilance system for the fulfilment of pharmacovigilance  
994 tasks equivalent to the relevant EU Member State's pharmacovigilance system. This includes the  
995 obligation to collect and collate all solicited and unsolicited reports of suspected adverse reactions,  
996 including those arising from errors with human medicinal products, and to evaluate all information  
997 scientifically, to consider options for risk minimisation and prevention and to take appropriate  
998 measures as necessary. As part of the pharmacovigilance system, the marketing authorisation holder  
999 shall operate a risk management system for each medicinal product and monitor the outcome of risk  
1000 minimisation measures which are contained in the risk management plan or which are laid down as  
1001 conditions of the marketing authorisation (Article 104 of Directive 2001/83/EC), including those  
1002 required to prevent or minimise the risk of medication errors.

1003 In line with the recommendations of GVP Module VII medication error reports not associated with an  
1004 adverse drug reaction should be included as a summary in the PSUR sub-section VII.B.5.9 2.  
1005 'Medication errors'. This summary could include relevant information on patterns of medication errors

1006 and potential medication errors based on periodic line listings of case reports which should be made  
1007 available by MAHs on request of the National Competent Authority or the Agency.

1008 In line with the recommendations of GVP Module V.B.8.6.4 risk management plan Part II, Module  
1009 SVI.4 "Potential for medication errors" should include a stand-alone summary of aggregated data on  
1010 medication errors which occurred during the clinical trial programme and/or post-marketing period.

1011 For this purpose it is paramount that MAHs systematically collect and evaluate scientifically reports of  
1012 medication errors which are brought to their attention which do not fall in the definition of a reportable  
1013 ICSR (i.e. intercepted errors, medication errors without harm and potential errors) and integrate  
1014 relevant information about the category (type) of error, the stage of medication process where the  
1015 error occurred, any contributing factors (e.g. human factors, healthcare system factors or external  
1016 factors) and mitigating factors (e.g. actions or circumstances which prevented or moderated the  
1017 progression of an error towards harming the patient) in the evaluation of the risk for the patient and  
1018 the appropriate risk minimisation measures(s). Further guidance on this issue is provided in the good  
1019 practice guide on the coding and reporting of medication errors.

## 1020 **7.5. European Medicines Agency**

1021 Within the EU, the responsibility for authorisation and supervision of medicinal products is shared  
1022 between the national competent authorities in EU Member States, the European Commission and the  
1023 European Medicines Agency, with the balance of responsibilities depending upon the route of  
1024 authorisation.

1025 For centrally authorised products Article 107(1) of Directive 2001/83/EC requires the Agency in  
1026 collaboration with EU Member States to monitor the outcome of risk minimisation measures contained  
1027 in the RMPs and of the conditions of marketing authorisation (particularly those for the safe and  
1028 effective use), to assess updates of the RMP and to monitor the data in the EV database to determine  
1029 whether there are new risks or whether the risk have changed and whether those risks impact on the  
1030 B/R balance (Article 107h(1) of Directive 2001/83/EC). Also MAHs, national competent authorities and  
1031 the Agency shall inform each other in the event of new risks or risks that have changed or changes to  
1032 the B/R balance.

1033 These provisions apply to any safety concern including medication errors identified in a risk  
1034 management plan for a medicinal product regardless of the route of authorisation.

## 1035 **Annex 1 – Sources of medication error in medicinal product** 1036 **design**

### 1037 *Tablets*

- 1038 • A large number of medicinal products are presented in tablet form, which can be associated with  
1039 several sources of error. Patients may take the wrong dose in situations where multiple tablet  
1040 strengths are available but presented in similar packaging and have a very similar appearance in  
1041 terms of colour, size and shape. Similar problems may occur when a product is available in  
1042 immediate-release and extended-release formulations but where the packaging and tablet  
1043 appearance are very similar. Some medicinal products require a loading dose to be used initially  
1044 and later replaced by a lower maintenance dose and adverse events may occur if this down-  
1045 titration of dose does not occur. Similarly, up-titration may be required with a lower dose used for  
1046 the first few weeks later replaced by a higher maintenance dose (e.g. initiation packs of retigabine  
1047 are used for 2 weeks to deliver the initiation dose of 100 mg, three times daily (a total of 300 mg a  
1048 day) which is gradually adjusted over the following weeks up to a maximum dose of up to 400 mg  
1049 three times daily (a total of 1,200 mg a day).
- 1050 • Some tablets include a score-line down the centre so that tablets can be broken into smaller doses,  
1051 but the tablets may be difficult to break or not break cleanly, meaning that broken tablets may not  
1052 provide the correct dose. Other tablets may not be suitable for breaking (such as those with an  
1053 enteric coating) but may be broken or cut and used by patients anyway.
- 1054 • The size of tablet may make the medicinal product difficult to swallow for some patients and other  
1055 tablets can be irritating to the oesophagus.
- 1056 • Tablets are usually presented within foil-sealed blisters or within foil pouches but brittle or fragile  
1057 tablets may break if pushed through foil too hard, which can be problematic if only part of the  
1058 tablet is taken or if the tablet should not have been crushed/broken (e.g. modified release  
1059 preparations). Blister packs may also be difficult to open for patients with dexterity problems with  
1060 the potential risk of injury from use of scissors or sharp objects to open the blister packs. Some  
1061 formulations are developed for oral administration but should not be swallowed, including sub-  
1062 lingual tablets, buccal tablets, melts and oro-dispersible tablets. These dissolve in the mouth,  
1063 under the tongue or inside the cheek (e.g. asenapine sublingual tablets are placed under the  
1064 tongue and allowed to dissolve; eating and drinking should be avoided for 10 minutes after  
1065 administration) but may not dissolve quickly or could be inadvertently swallowed instead of slowly  
1066 dissolving, which may affect absorption and efficacy.
- 1067 • Some tablets are presented as effervescent formulations which must be dissolved in water before  
1068 use but these could be crushed instead of dissolved and attempts may be made to dissolve  
1069 (unsuccessfully) in liquids other than water.

### 1070 *Capsules*

- 1071 • Medicinal products are commonly presented in capsule formulations. Capsule shells are often made  
1072 of gelatine which can become brittle if exposed to the air for a long time or if the foil is removed  
1073 from blister packs too far in advance of use of the capsule. Capsules may be opened and the  
1074 contents sprinkled onto food but this may not be appropriate where the capsule contents may be  
1075 irritating to the oesophagus. A number of respiratory medicinal products are presented in capsule  
1076 form with the contents of the capsules inhaled through a device; such products may inadvertently  
1077 be swallowed by patients.

### 1078 *Oral solutions and suspensions*

1079 • Solutions or suspensions may require use of dosing devices and these can be associated with  
1080 problems; liquid medicinal products measured into plastic dosing spoons can develop a meniscus  
1081 which can lead to overdosing and potentially less desirable than a graduated syringe. Liquid  
1082 formulations are also likely to be presented with child-resistant-closures to reduce the risk of  
1083 children accidentally ingesting the medicine within but these can be difficult to open for patients with  
1084 manual dexterity problems.

1085 • Suspensions require shaking to produce homogenous solution before dosing and this is not always  
1086 made clear

#### 1087 *Other orally administered formulations*

1088 • Some dose forms have been developed for ease of use or administration but these may present  
1089 hazards. These include dose forms such as lozenges with integral oro-mucosal applicator or which  
1090 have been developed to be chewable and palatable, which could be mistaken for sweets by  
1091 children (e.g. fentanyl 'lollies'). Similarly, medicated chewing gum (e.g. nicotine replacement  
1092 therapy) may be mistaken for regular chewing gum which could expose users (and especially  
1093 children) to potential harmful doses of nicotine.

#### 1094 *Patches*

1095 • The use of medicated patches has increased in recent years but these too may be associated with  
1096 medication errors. Patches may be difficult to locate or identify in situ leading to inadvertent  
1097 overdose if more patches are applied than is recommended or if patches are left on the skin for  
1098 longer than directed (e.g. as occurred with rivastigmine patches, reported in June 2010)

1099 • Patches which are still pharmaceutically active may become accidentally stuck to other people  
1100 (who are then exposed in error). This has occurred with fentanyl patches where in the US, up to  
1101 April 2012 thirty cases of paediatric accidental exposure were identified, with children coming into  
1102 contact with patches that were loosely attached to or had fallen off of the intended wearer, or that  
1103 were stored or disposed of improperly; 10 of these cases resulted in death. There have also been  
1104 instances where discarded patches have been thrown away and eaten by children.

1105 • Patches may be adhered to non-recommended sites which may expose users to a higher dose than  
1106 intended and cutting the patch into several pieces for ease of application may reduce the dose and  
1107 efficacy or may cause the patch not to work at all.

1108 • There have also been reports of patches containing metal as part of the adhesive backing causing  
1109 skin burns when worn during MRI scans.

#### 1110 *Suppositories*

1111 • Non-parenteral formulations such as suppositories and pessaries may be accidentally eaten instead  
1112 of being inserted, and may also be used at the wrong sites.

#### 1113 *Implants*

1114 • Some products are implanted into the body (e.g. contraceptive implants for insulin infusion pumps)  
1115 and there may be errors associated with the insertion of the device or its removal, insertion in the  
1116 wrong place (e.g. dexamethasone eye implant misplacement), devices moving or breaking  
1117 internally (and perforating tissues), or becoming difficult to locate.

1118 •

#### 1119 *Topical products*

1120 • Topically-applied medicinal products may include those intended for use on the skin or in the eyes  
1121 or for rectal or vaginal use via an applicator and the design of the container (or applicator, or both)  
1122 is important to ensure these can be applied safely and at the correct dose. Eye drops are often  
1123 presented in a bottle or individual single-use droppers but these can be difficult to hold and use for  
1124 patients with manual dexterity problems. Related to this, single-use droppers which are broken  
1125 open to use may leave sharp edges which could damage the cornea (e.g. as with timolol and  
1126 dorzolamide eye drops after the introduction of a new design of dropper, reported in July 2013).  
1127 For drops presented in larger bottles, instructions for use vary and patients may squeeze the bottle  
1128 excessively and deliver an overdose, which could have serious consequences particularly if  
1129 administered at a too-high dose for a prolonged period.

#### 1130 *Aerosols and inhaled medicinal products*

- 1131 • Some medicinal products are presented as an aerosol spray which could get into the eyes or  
1132 irritate damaged or broken skin. A common error with orally inhaled medicines presented in  
1133 aerosol form (a pressurised metered dose inhaler, pMDI) is patients' difficulty synchronising  
1134 inspiration with inhaler activation, meaning that a full dose may not be inhaled and the medicinal  
1135 product may be largely deposited in the mouth instead. By contrast, breath-actuated dry powder  
1136 inhalers (DPI) do not require careful timing of actuation and inspiration. However, since DPI rely on  
1137 inspiratory airflow, these may be more difficult to use and be less efficacious for patients with poor  
1138 respiratory airflow.
- 1139 • There are a broad range of inhaler devices available and all differ in their design and function with  
1140 the potential for misunderstanding of their operation. Most pMDI require shaking of the container  
1141 to mix then pressing of a button to actuate while multiple dose DPIs require 'priming' by pressing a  
1142 button, sliding a lever or twisting the base of the inhaler. For multiple dose-unit DPIs, the  
1143 medicinal product inside must be regularly replaced. Inhalers may stop working altogether if  
1144 dropped accidentally and where devices do not have a dose counter available it can be difficult to  
1145 tell when the inhaler is empty.
- 1146 • Inhalers frequently have a dust cap in place to protect the mouth piece but if this is absent, foreign  
1147 bodies may enter the mouthpiece of the inhaler and be inhaled or swallowed when the medicinal  
1148 product is next used.
- 1149 • Medicinal products given via nebulisers may accidentally get into the eyes if a face mask system is  
1150 used, or the nebuliser may become contaminated if not cleaned properly or if the medicinal  
1151 products used in it are not handled correctly.

#### 1152 *Parenteral medicinal products*

- 1153 • Parenteral products which require dilution before use may be presented in an apparently ready-to-  
1154 use form and could lead to use of a concentrated dose. Some medicinal products requires a  
1155 number of diluting steps to achieve the final solution for injection (e.g. mycophenolate mofetil  
1156 requires a reconstitution step followed by a dilution step, both with 5% Dextrose Injection USP,  
1157 prior to use) which increases the number of stages at which errors in dilution could be made.  
1158 Products requiring reconstitution are often presented as a powder or concentrate along with a  
1159 solvent/diluent and it is possible that a concentrate-solvent mixture with an unintended  
1160 concentration may be achieved if the wrong amounts of concentrate and diluent are mixed. This  
1161 can particularly occur if the solvent vial and the concentrate vial each contain an overfill to  
1162 compensate for liquid lost during the initial dilution process but the contents are not entirely  
1163 mixed. There may be confusion over appropriate dosing when products are provided as  
1164 concentrations, with difficulties calculating the correct dose in mg/ml or ml/kg for solutions  
1165 presented as a w/v% concentration.



1166 *Presentation of the medicinal products*

- 1167 • The closure system for containers may be a source of error if solutions intended for topical or oral use  
1168 are presented in the same way and mistaken for products for injection. Some medicinal products are  
1169 presented in a ready to use syringe but the potential for errors can arise if multiple strengths of a  
1170 product are presented in a syringe with an identical fill volume.

1171 *Examples of medication errors involving Devices*

- 1172 • Patient received a 100 x overdose and died as a result of an insulin product being measured and  
1173 administered using a 2ml intravenous syringe instead of a insulin syringe.
- 1174 • Patient received a 5ml dose of oral antibiotic syrup intravenously as a result of the dose being  
1175 measured and administered using a 5ml intravenous syringe instead of an oral/enteral syringe.
- 1176 • Patient received a subcutaneous injection of adrenaline into the thumb rather than into the  
1177 required site of administration due to confusion over how to operate a prefilled syringe device.
- 1178 • A patient did not receive their required palliative care analgesic subcutaneous infusion for 6 hours,  
1179 as a result of the nurse not correctly operating the syringe driver and setting a rate of infusion of  
1180 0ml over 12 hours.
- 1181 • A paediatric patient received an overdose of infusion fluid as a result of an adult intravenous  
1182 administration set being used instead of a paediatric administration set being used, where 20 drops  
1183 = 1ml instead of 60 drops = 1ml and the wrong rate of administration was set by gravity infusion.
- 1184 • A patient became hypoglycaemic and died as a result of receiving treatment for hypercalcaemia  
1185 when an insulin infusion was administered by syringe driver, and the glucose 10% infusion that  
1186 should have been administered at the same time was turned off by accident.
- 1187 • An overdose of vasopressor infusion occurred as a result of the volumetric infusion pump being  
1188 mis-programmed at 100ml/hour instead of 10ml/hour.
- 1189 • A 30ml syringe was used in a syringe driver pump instead of a 50ml syringe resulting in a  
1190 overdose of a vasodilator infusion.
- 1191 • The patient blood pressure failed to be controlled adequately as a result of a normal intravenous  
1192 administration set being used in the volumetric infusion pump instead of a low adsorption set  
1193 recommended by the manufacturer.
- 1194 • A patient experienced severe phlebitis as a result of the intravenous antifungal infusion not being  
1195 administered via a filter, as recommended by the manufacturer.
- 1196 • A patient with obstructive airways disease being treated with nebulised beta agonists went into  
1197 respiratory failure as a result of the nebuliser device used to administer his therapy being powered  
1198 by oxygen gas rather than medical air.
- 1199 • A patient with obstructive airways disease being treated with oxygen therapy went into respiratory  
1200 failure because a venturi mask delivering the wrong percentage of oxygen was used.

1201

1202 **Annex 2 – Design features which should be considered to**  
1203 **reduce the risk of medication error**

1204 *Tablets*

- 1205 • Tablets should differ in size, shape and/or colour and have clear markings if they are of different  
1206 strengths, or are available in immediate- and modified-release formulations, or are different  
1207 generic formulations of a particular substance
- 1208 • Colour conventions should be followed where these have been agreed for a class or group of  
1209 medicinal products (e.g. colour coding in the UK for different strengths of warfarin tablets,  
1210 applicable to all manufacturers)

1211 **Figure 1: different strengths of warfarin**



- 1213 • Any score-lines for ease of breaking should result in a clean break and tablets that should not be  
1214 broken or crushed should not be scored or an easy shape to break; equally, tablets that can be  
1215 chewed or crushed without affecting efficacy or causing harm to the patient should be clearly  
1216 labelled as such
- 1217 • Tablets which are irritating to the oesophagus should be accompanied by clear instructions for use  
1218 on avoiding harm (e.g. take with a full glass of water and patient instructed not to lie down after  
1219 taking (e.g. alendronate))
- 1220 • tablets which have proven difficult to swallow due to size or coating should be reformulated where  
1221 possible
- 1222 • Tablets/capsules presented in blister packs or in foil should be reformulated where possible to  
1223 make them less friable and prone to breaking; if this is not possible, clear instructions for handling  
1224 of the tablets (e.g. instructions not to push the tablets/capsules through the foil, or to peel back  
1225 foil covering and remove the tablet from the blister) should be included and blister packs should be  
1226 designed so that they are easy to open

1227 *Capsules*

- 1228 • Most capsule shells are made of gelatin but other materials (e.g. hypromellose) are available and  
1229 may be more suitable than gelatin, particularly if they encapsulate particularly hygroscopic  
1230 substances
- 1231 • Labelling should highlight the importance of not exposing capsules to air until they are  
1232 administered and not opening capsules before use (unless this is an approved way to use the  
1233 medicine, e.g. sprinkling on food)
- 1234 • Respiratory medicinal products presented in capsule form should carry clear instructions on using  
1235 the capsule with the inhaler device, that the capsule should not be swallowed and that only the  
1236 approved inhaler device should be used to deliver the medicinal product

1237 *Other orally administered formulations*

- 1238 • Medicinal products which dissolve on or under the tongue or in the cheek should be accompanied  
1239 by clear instructions that the product is now intended to be swallowed and for how long the  
1240 medicinal product should be left in place
- 1241 • Medicinal products which may be mistaken for sweets should be packaged very plainly and should  
1242 carry instructions to keep in a locked container out of reach of children
- 1243 • Effervescent formulations should carry clear labelling on what fluids they can be dissolved in and  
1244 how long they should be left to dissolve before taking
- 1245 *Patches*
- 1246 • Patches should carry clear labelling on where they should be applied, how long they should be  
1247 applied for, whether they can be cut into smaller sizes and clear instructions on the proper and  
1248 safe disposal of the patches (e.g. they should be folded so that the adhesive side of the patch  
1249 adheres to itself and then they should be safely discarded)
- 1250 • Patches should be a visible colour or patterned (i.e. not skin-coloured or clear) so they can be  
1251 clearly seen on the skin and are highly visible if they become detached and drop onto the floor.  
1252 This is particularly important for products which are particularly dangerous in overdose (e.g.  
1253 fentanyl patches)
- 1254 • If patches contain metal foil or parts, this should be clearly indicated in labelling along with a  
1255 warning that such patches should be removed in case of a MRI scan
- 1256 *Suppositories, pessaries and implants*
- 1257 • Suppositories and pessaries should be accompanied by clear instructions for use and a clear  
1258 statement that they should not be swallowed or placed in the mouth
- 1259 • Clear instructions (including pictures) for handling, insertion, placement, checking of correct siting  
1260 and removal of implants should be included in product information
- 1261 • Implants should be reformulated as necessary to include tracers allowing for detection by x-ray or  
1262 other means (e.g. replacement of Implanon with Nexplanon, which has had barium sulphate added  
1263 to make it radio-opaque)
- 1264 *Solutions, suspensions and topically-applied liquids*
- 1265 • Liquid medicinal products (especially for children) should be supplied with an appropriate  
1266 graduated measuring device, such as an oral or enteral dosing syringe (that cannot be connected  
1267 to intravenous catheters or ports), dropper dosing cup or spoon. Oral liquid medicinal products  
1268 with a narrow therapeutic index should preferably be provided with a dosing syringe.
- 1269 • Liquid medicines for patients with manual dexterity problems (e.g. rheumatoid arthritis) should be  
1270 presented in containers with medigrip lids or if child-resistant closures (CRC) are necessary, CRCs  
1271 with keys (which still allow ease of opening)
- 1272 • Single-use eye droppers should be designed in such a way that there are no sharp edges after  
1273 opening
- 1274 • Bottles containing eye drops should be accompanied by clear instructions (including diagrams) on  
1275 how to administer the drops and the importance of not squeezing the bottle if this is not how the  
1276 drops should be dispensed from the bottle
- 1277 *Aerosols and inhaled medicinal products*

- 1278 • Clear instructions for use of inhalers (including diagrams) should be included in product information  
 1279 and along with a reminder that patients should be shown how to use the device and that their  
 1280 inhaler technique should be checked regularly
- 1281 • Inhaled steroid medicines should be accompanied by a recommendation to rinse out the mouth  
 1282 after use to reduce the risk of oral candidiasis
- 1283 • MAHs intending to market medicinal products presented as a pMDI should ensure that data on use  
 1284 with an appropriate spacer device is collected and seek authorisation in conjunction with a spacer  
 1285 device; and product information should include advice on spacers where this is approved as part of  
 1286 the SmPC
- 1287 • Inhalers with removable dust caps over the mouthpiece should include a reminder in the PL that  
 1288 the dust cap should be replaced when the product is not in use
- 1289 • Solutions for use with a nebuliser should be accompanied by clear instructions for use with various  
 1290 types of nebuliser (jet and ultrasonic) and steroids and antibiotics for use with a nebuliser should  
 1291 include a warning not to use with a facemask to avoid contact with the eyes and skin of the face
- 1292 *Products for IV use or parenteral administration*
- 1293 • The authorised route(s) of administration should be clearly stated in the product information
- 1294 • Product information should describe suitable solvents and diluents if supplied as a powder or  
 1295 concentrate for reconstitution; Products which require dilution should have this clearly marked on  
 1296 the immediate label along with any incompatibilities
- 1297 • Where products consisting of a concentrate and solvent contain an overfill to compensate for liquid  
 1298 lost during the dilution process, labelling should indicate clearly that the entire contents of the  
 1299 solvent vial must be added to the concentrate vial
- 1300 • Instructions for use for IV medicines should include clear instructions on the time over which the  
 1301 product should be administered or else a clear statement that a bolus dose may be given
- 1302 • If a medicinal product has to be administered within a specific time after reconstitution or dilution  
 1303 this should be noted in product information
- 1304 • Information on the appropriate dilution of solutions should be included in the SmPC and products  
 1305 requiring dilution require a Technical Information Leaflet (TIL) for use by HCPs to accompany the  
 1306 PIL; information on dilution should be described in the TIL.
- 1307 *General considerations*
- 1308 • Medicines for acute use in emergency situations should be presented in a ready-to-use format  
 1309 without the need for measuring of doses or solutions
- 1310 • Where a single substance is available as different branded products or where different strengths  
 1311 have different indications, product information should highlight clearly any differences in posology  
 1312 (e.g. daily vs weekly administration of insulin analogues), composition (e.g. different excipients<sup>30</sup>,  
 1313 some of which such as milk proteins, peanut oil may cause allergies), or strength (hybrid  
 1314 applications).
- 1315 • Biosimilar products should be clearly differentiated from each other by use of distinguishing  
 1316 packaging and prescribed by brand name rather than by INN to minimise inadvertent switching  
 1317 between products and to allow for effective Pharmacovigilance.

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<sup>30</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003412.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf)