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7 requirements of the applicable statutes,
8 regulations, or both.

9 **GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN** 10 **PHARMACEUTICALS**

11 **1. INTRODUCTION**

12 **1.1. Objectives Of The Guideline**

13 This guideline was developed to help protect clinical trial participants and patients
14 receiving marketed products from potential adverse reactions to pharmaceuticals,
15 while avoiding unnecessary use of animals and other resources.

16 This guideline defines safety pharmacology and describes general principles and
17 recommendations for its evaluation.

18 **1.2 Background**

19 Pharmacology studies have been performed worldwide for many years as part of the
20 non-clinical evaluation of pharmaceuticals for human use. There have been, however,
21 no internationally accepted definitions, objectives or recommendations on the design
22 and conduct of safety pharmacology studies. (Note 1)

23 In the ICH non-clinical safety guidelines, the term "safety pharmacology studies" first
24 appeared in the topics, "Timing of Non-clinical Safety Studies for the Conduct of
25 Human Clinical Trials for Pharmaceuticals (M3)" and "Preclinical Safety Evaluation of
26 Biotechnology-derived Pharmaceuticals (S6)" as studies that should be conducted prior
27 to the initiation of clinical trials (1, 2). Details of the safety pharmacology studies,
28 including their definition and objectives, were left for future discussion.

29 **1.3 Scope Of The Guideline**

30 This guideline generally applies to new chemical entities and biotechnology-derived
31 products for human use. This guideline may be applied to marketed pharmaceuticals
32 when appropriate (e.g. when adverse clinical events, a new patient population or route
33 of administration raise concerns not previously addressed).

34 **1.4 General Principle**

35 It is important to adopt a rational approach when selecting and conducting safety
36 pharmacology studies. The specific studies that should be conducted and their design
37 will vary based on the individual properties and intended uses of pharmaceuticals.
38 Scientifically valid methods should be used, and when there are internationally
39 recognized methods that are applicable to pharmaceuticals, these are preferable.
40 Moreover, the use of new technologies and methodologies in accordance with sound
41 scientific principles is encouraged.

39 Certain endpoints may not need separate evaluation in safety pharmacology studies,
40 while in other cases safety pharmacology endpoints may be incorporated in the design
41 of other studies (e.g. toxicology, kinetic or clinical studies). Although adverse effects of
42 a substance may be detectable at exposures that fall within the therapeutic range in
43 appropriately designed safety pharmacology studies, they may not be evident from
44 observations and measurements used to detect overt toxicity in conventional animal
45 toxicity studies.

46 **1.5 Definition Of Safety Pharmacology**

47 Pharmacology studies can be divided into three categories: primary pharmacodynamic,
48 secondary pharmacodynamic and safety pharmacology studies. (See Note 2 for
49 definitions of primary pharmacodynamic and secondary pharmacodynamic studies.)

50 For the purpose of this document, safety pharmacology studies are defined as those
51 studies that investigate the potential undesirable pharmacodynamic effects of a
52 substance on physiological functions in relationship to exposure.

53 In some cases, information on the primary and secondary pharmacodynamic
54 properties of the substance may contribute to the safety evaluation for potential
55 adverse effect(s) in humans and should be considered along with the findings of safety
56 pharmacology studies.

57 **2. GUIDELINE**

58 **2.1 Objectives Of Studies**

59 The objectives of safety pharmacology studies are: 1) to identify undesirable
60 pharmacodynamic properties of a substance that may have relevance to its human
61 safety; 2) to evaluate adverse pharmacodynamic and/or pathophysiological effects of a
62 substance observed in toxicology and/or clinical studies; and 3) to investigate the
63 mechanism of the adverse pharmacodynamic effects observed and/or suspected. The
64 investigational plan to meet these objectives should be clearly identified and
65 delineated.

66 **2.2 General Consideration In Selection And Design Of Safety** 67 **Pharmacology Studies**

68 Since pharmacological effects vary depending on the specific properties of each test
69 substance, the studies should be selected and designed accordingly. The following
70 factors should be considered (the list is not comprehensive):

- 71 (1) Effects related to the therapeutic class of the test substance, since the mechanism
72 of action may suggest specific adverse effects (e.g. proarrhythmia is a common
73 feature of antiarrhythmic agents);
- 74 (2) Adverse effects associated with members of the chemical or therapeutic class, but
75 independent of the primary pharmacodynamic effects (e.g. anti-psychotics and QT
76 prolongation);
- 77 (3) Ligand binding or enzyme assay data suggesting a potential for adverse effects;
78 and
- 79 (4) Data from previous safety pharmacology studies, from secondary
80 pharmacodynamic studies, from toxicology studies, or from human use, that
81 warrant further investigation to establish and characterize their relevance to

82 potential adverse reactions in humans.

83 During early development, sufficient information (e.g. comparative metabolism) may
84 not always be available to rationally select or design the studies; in such a
85 circumstance, a more general screening approach may be applied.

86 A hierarchy of organ systems can be developed according to their importance with
87 respect to life-supporting functions. Organs or systems acutely necessary for life, i.e.,
88 the cardiovascular, respiratory and central nervous systems, are considered to be the
89 most important ones to assess in safety pharmacology studies. Other organ systems,
90 the functions of which can be transiently disrupted by adverse pharmacodynamic
91 effects without causing irreversible harm, are of less immediate investigative concern.

92 Safety pharmacology evaluation of effects on systems other than the above vital
93 systems may also be of particular importance when considering factors such as the
94 likely clinical trial or patient population (e.g. gastrointestinal tract in Crohn's disease,
95 immune system in immune compromised patients.)

96 **2.3 Test Systems**

97 **2.3.1 General Considerations On Test Systems**

98 Careful consideration should be given to the selection of relevant animal models or
99 other test systems so that scientifically valid information can be derived. Selection
100 criteria include the pharmacodynamic responsiveness of the model, pharmacokinetic
101 profile, species, strain, gender and age of the experimental animals, the susceptibility,
102 sensitivity, and reproducibility of the test system and available background data on
103 the substance. Data from humans (e.g. in vitro metabolism), when available, should be
104 also considered in the test system selection. The time points for the measurements
105 should be based on pharmacodynamic and pharmacokinetic considerations.
106 Justification should be provided for the selection of the particular animal model or test
107 system.

108 **2.3.2 Use Of In Vivo And In Vitro Studies**

109 Animal models and/or ex vivo/in vitro preparations, isolated organs and tissues may be
110 used. In vitro systems may further include but are not limited to: cell cultures,
111 cellular fragments/subcellular organelles, receptors, channels, transporters and
112 enzymes. In vitro systems may be utilized in supportive studies (e.g. to obtain a
113 profile of the activity of the substance or to investigate the mechanism of effects
114 observed in vivo).

115 In conducting in vivo studies on vital functions, it is preferable to use unanesthetized
116 animals. Data from unrestrained animals that may be chronically instrumented for
117 telemetry, other suitable instrumentation methods for conscious animals, or animals
118 conditioned to the laboratory environment are preferable to data from restrained or
119 unconditioned animals. In the use of unanesthetized animals the avoidance of
120 discomfort or pain is a foremost consideration.

121 **2.3.3 Experimental Design**

122 **2.3.3.1 Sample Size And Use Of Controls**

123 The number of animals or isolated preparations should be adequate to clearly
124 demonstrate the presence or absence of an effect of the test substance. This should
125 take into consideration the size of biological effect that is of concern. Appropriate
126 negative and positive control groups should be included in the experimental design. In
127 well-characterized in vivo test systems, positive controls may not be necessary. The
128 exclusion of controls from studies should be justified.

129 **2.3.3.2 Route Of Administration**

130 In general, the expected clinical route of administration should be used when feasible.
131 Regardless of the route of administration, exposure to the parent substance and its major
132 metabolites should be at least similar to or greater than that achieved in humans when
133 such information is available. Assessment of effects by more than one route may be
134 appropriate if the test substance is intended for clinical use by more than one route of
135 administration (e.g. oral and parenteral), or where there are observed or anticipated
136 significant qualitative and quantitative differences in systemic or local exposure.

137 **2.4 Dose Levels Or Concentrations Of Test Substance**

138 **2.4.1 In Vivo Studies**

139 Safety pharmacology studies should be designed to define the dose response curve of
140 the adverse effects. The time course (e.g. onset and duration of response) of the effects
141 should be investigated when feasible. Generally, the dose response for the adverse
142 effects should be compared to doses necessary for the primary pharmacodynamic
143 response in the test species or the proposed therapeutic effect in humans, if feasible. It
144 is recognized that there are species differences in pharmacodynamic sensitivity.
145 Therefore, doses should include and exceed the primary pharmacodynamic or
146 therapeutic range. In the absence of adverse effects on safety pharmacology
147 parameters, the highest tested dose should equal or exceed those doses producing
148 some adverse effects in studies of similar route and duration. These adverse effects
149 may include dose-limiting pharmacodynamic effects or other toxicity. In practice,
150 some effects in the toxic range (e.g. tremors or fasciculations during ECG recording)
151 may confound the interpretation of safety pharmacology effects and may also limit
152 dose levels. Testing of a single dose group may be appropriate in the absence of a
153 specific adverse effect in the test species.

154 **2.4.2 In Vitro Studies**

155 In vitro studies should be designed to establish an effect-concentration relationship. A
156 range of concentrations should be explored in order to increase the likelihood of
157 detecting an effect on the test system.

158 **2.5 Duration Of Dosing**

159 Safety pharmacology studies are generally performed by single dose administration.
160 When results from repeat dose non-clinical studies or human use give rise to concerns
161 about safety pharmacological effects, the duration of the safety pharmacology studies
162 to address these effects should be rationally based.

163 **2.6 Studies On Metabolites, Isomers And Finished Products**

164 Generally, any parent compound and its major metabolite(s) that achieve systemic
165 exposure or are expected to reach the systemic circulation in humans should be
166 evaluated in safety pharmacology studies. Evaluation of such effects of major
167 metabolites is often accomplished through studies of the parent compound in intact
168 animals. If the major human metabolite(s) is (are) found to be absent or present only
169 at relatively low concentrations in animals, assessment of the effects of such
170 metabolite(s) on safety pharmacology functions should be considered. When
171 metabolites from humans are known to substantially contribute to the
172 pharmacological actions of the parent compound, it may be important to test such
173 active metabolites. When the *in vivo* studies on the parent compound have not
174 adequately assessed metabolites, the tests of metabolites may often use *in vitro*
175 systems based on practical considerations.

176 *In vitro* or *in vivo* testing of the individual isomers should also be considered when the
177 product contains the mixture.

178 Safety pharmacology studies with the finished product formulation(s) are only
179 necessary for formulations that substantially alter the pharmacokinetics and/or
180 pharmacodynamics of the active substance in comparison to those previously tested
181 (i.e. through active excipients such as penetration enhancers, liposomes, and other
182 changes such as polymorphism).

183 **2.7 Safety Pharmacology Core Battery**

184 The purpose of the safety pharmacology core battery is to investigate the effects of the
185 test substance on vital functions. In this regard, the cardiovascular, respiratory and
186 central nervous systems are usually considered the vital organ systems that should be
187 studied in the core battery. In some instances, based on scientific rationale, the core
188 battery may need to be supplemented (see also section 2.8) or may not need to be
189 implemented (see also section 2.9).

190 The exclusion of certain test(s) or exploration(s) of certain organs, systems or functions
191 should be scientifically justified.

192 **2.7.1 Central Nervous System**

193 Effects of the test substance on the central nervous system should be assessed
194 appropriately. Motor activity, behavioral changes, coordination, sensory/motor reflex
195 responses and body temperature should be evaluated. For example, a functional
196 observation battery (FOB) (3), modified Irwin's (4), or other appropriate test (5) may
197 be used.

198 **2.7.2 Cardiovascular System**

199 Effects of the test substance on the cardiovascular system should be assessed
200 appropriately. Blood pressure, heart rate, and the electrocardiogram should be

201 evaluated. In vitro and/or ex vivo methods including electrophysiology should also be
202 considered. (Note 3)

203 **2.7.3 Respiratory System**

204 Effects of the test substance on the respiratory system should be assessed
205 appropriately. Respiratory rate and depth should be evaluated. In most cases, clinical
206 observation of animals to assess these parameters should be adequate, while in other
207 instances (e.g. pharmaceuticals targeting or directly delivered to the respiratory
208 system) instrumented methods may be preferable.

209 **2.8 Safety Pharmacology Studies Conducted as Necessary**

210 Adverse reactions may be suspected based on the pharmacological properties of the
211 test substance. Additionally, concerns may arise from the safety pharmacology core
212 battery, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or
213 from literature reports. When such potential adverse reactions raise concern for
214 human safety, then these should be explored in follow-up or supplemental safety
215 pharmacology studies, as appropriate.

216 **2.8.1. Follow-up Studies For Safety Pharmacology Core Battery**

217 Follow-up studies are meant to provide a greater depth of understanding than, or
218 additional knowledge to, that provided by the core battery on vital functions. The
219 following lists are not meant to be comprehensive or prescriptive, and the test systems
220 are decided on a case-by-case basis after considering factors such as existing non-
221 clinical or human data. In some cases, it may be more appropriate to address these
222 effects in the conduct of other non-clinical and/or clinical studies.

223 **2.8.1.1 Central Nervous System**

224 Behavioral pharmacology, learning and memory, specific ligand binding,
225 neurochemistry, visual, auditory and/or electrophysiology examinations etc.

226 **2.8.1.2 Cardiovascular System**

227 Cardiac output, ventricular contractility, vascular resistance, the effects of
228 endogenously released and/or exogenously administered neurotransmitters on the
229 cardiovascular responses etc.

230 **2.8.1.3 Respiratory System**

231 Tidal volume, bronchial resistance, compliance, pulmonary arterial pressure, blood gases
232 etc.

233 **2.8.2 Supplemental Safety Pharmacology Studies**

234 Supplemental studies are meant to evaluate organ system functions not addressed by
235 the core battery or repeated dose toxicity studies when there is a cause for concern.

236 **2.8.2.1 Renal/Urinary System**

237 Effects of the test substance on relevant renal parameters should be assessed. For
238 example, urinalysis including data for volume, specific gravity, osmolality, pH,
239 fluid/electrolyte balance, proteins, cytology and blood chemistry determinations such
240 as BUN, creatinine and plasma proteins may be used.

241 **2.8.2.2 Autonomic Nervous System**

242 Effects of the test substance on the autonomic nervous system should be assessed. For
243 example, binding to receptors relevant for the autonomic nervous system, agonist or
244 antagonist responses *in vivo* or *in vitro*, direct stimulation of autonomic nerves and
245 measurement of cardiovascular responses, baroreflex testing, and heart rate
246 variability may be used.

247 **2.8.2.3 Gastrointestinal System**

248 Effects of the test substance on the gastrointestinal system should be assessed. For
249 example, gastric secretion, gastrointestinal injury potential, bile secretion, transit
250 time *in vivo*, ileal contraction *in vitro*, gastric pH measurement and pooling may be
251 used.

252 **2.8.2.4 Other Organ Systems**

253 Effects of the test substance on organ systems not investigated elsewhere should be
254 assessed when there is a reason for concern. For example, dependency potential,
255 skeletal muscle, immune and endocrine functions may be investigated.

256 **2.9 Conditions Under Which Studies Are Not Necessary**

257 Safety pharmacology studies may not be necessary for locally applied agents (e.g.
258 dermal or ocular) where the pharmacology of the test substance is well characterized,
259 and where systemic exposure or distribution to the vital organs is demonstrated to be
260 low.

261 Safety pharmacology studies prior to the first administration in humans may not be
262 necessary for cytotoxic agents for treatment of end-stage cancer patients. For
263 cytotoxic agents with novel mechanisms of action, there may be value in conducting
264 safety pharmacology studies.

265 Safety pharmacology core battery studies may be reduced or eliminated for
266 biotechnology-derived products that achieve highly specific receptor targeting. In this
267 case, relevant safety pharmacology endpoints should be evaluated in toxicology and/or
268 pharmacodynamic studies.

269 There may be additional exceptions where safety pharmacology testing is not
270 necessary, for example, in the case of a new salt having similar pharmacokinetics and
271 pharmacodynamics.

272 **2.10 Timing Of Safety Pharmacology Studies In Relation To Clinical**
273 **Development**

274 When planning a safety pharmacology program Section 2.9 should be reviewed to
275 determine whether or not specific studies are necessary,.

276 **2.10.1 Prior To First Administration In Humans**

277 The effects of a test substance on the functions listed in the safety pharmacology core
278 battery should be investigated prior to first administration in humans. Any follow-up or
279 supplemental studies identified as necessary based on a cause for concern should also be
280 conducted. Information from toxicology studies adequately designed and conducted to
281 address safety pharmacology endpoints may reduce or eliminate the need for separate
282 safety pharmacology studies.

283 **2.10.2 During Clinical Development**

284 Additional investigations may be warranted to clarify observed or suspected adverse
285 effects in animals and humans during clinical development.

286 **2.10.3 Before Approval**

287 Safety pharmacology effects on systems listed section 2.8 should be assessed prior to
288 approval unless not warranted, in which case this should be justified. Available
289 information from toxicology studies adequately designed and conducted to address
290 safety pharmacology endpoints, or information from clinical studies, may support this
291 assessment and replace safety pharmacology studies.

292 **2.11 Application Of Good Laboratory Practices**

293 It is important to ensure the quality and reliability of the studies. This is normally
294 accomplished through the conduct of the studies according to GLP. Due to the unique
295 design of some safety pharmacology studies it may not be feasible to conduct these in
296 accordance with GLP. It has to be emphasized that data quality and integrity in
297 safety pharmacology studies should be assured even in the absence of formal
298 adherence to the GLP Principles. When studies are not conducted in accordance with
299 GLP, study reconstruction should be assured through adequate documentation of
300 study conduct, including archiving of data. Any study or study component not
301 conducted according to GLP should be adequately justified and the potential impact on
302 evaluation of the endpoint should be explained.

303 The safety pharmacology core battery is normally conducted under GLP. Follow-up
304 and supplemental studies should be conducted in accordance with GLP to the greatest
305 extent feasible. Safety pharmacology investigations can be part of toxicology studies;
306 in such cases these studies would be conducted in accordance with GLP.

307 Primary pharmacodynamic studies do not need to be conducted according to GLP.

308 Secondary pharmacodynamic studies, where their objectives differ from safety
309 pharmacology studies, do not need to be conducted according to GLP.

310 Safety pharmacology studies conducted as general screens in the absence of specific
311 cause for concern do not need to be conducted according to GLP.

312 **3. NOTES**

313 1. General pharmacology studies have been considered an important component in
314 drug safety assessment. General pharmacology studies were originally referred to as

315 those designed to examine effects other than the primary therapeutic effect of a drug
316 candidate. Safety pharmacology studies were focused on identifying adverse effects on
317 physiological functions. All three regions have accepted data from general
318 pharmacology studies (Japan and EC) or safety pharmacology studies (USA) in the
319 assessment of a marketing application. The Japanese Ministry of Health and Welfare
320 (MHW) issued the “*Guideline for General Pharmacology* “ in 1991. In this MHW
321 guideline, general pharmacology studies include those designed to identify unexpected
322 effects on organ system function, and to broaden pharmacological characterization
323 (pharmacological profiling). However there has been no internationally accepted
324 definition of the terms “primary pharmacodynamics”, “secondary pharmacodynamics”
325 and “safety pharmacology”. The need for harmonization of the nomenclature and the
326 development of an international guideline for safety pharmacology has been
327 recognized.

328 2. Studies on the mode of action and/or effects of a substance in relation to its desired
329 therapeutic target are primary pharmacodynamic studies. Studies on the mode of
330 action and/or effects of a substance not related to its desired therapeutic target are
331 secondary pharmacodynamic studies (these have sometimes been referred to as
332 general pharmacology studies).

333 3. More specific detailed guidance may follow as an Annex to this document as the
334 science progresses. Submission of data to support the use of these methods is
335 encouraged.

336 **4. REFERENCES**

- 337 1) ICH Harmonized Tripartite Guideline (M3) “Timing of Non-clinical Safety Studies
338 for the Conduct of Human Clinical Trials for Pharmaceuticals” (1997)
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