



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Examples of key binding elements in the PIP decisions

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Type of request	Description (example)	Comments
General	Development of an age-appropriate pharmaceutical form and/or strength [without specifying details, meaning composition, strengths, etc.]	<p>These requests are very general and do not specify any details of the pharmaceutical form and/or strength to be developed.</p> <p>Such requests could be accompanied by additional request to contact the PDCO when information about the pharmaceutical form to be developed and its composition and/or strength become available.</p> <p>This type of general request may be used in cases of early development when only limited information is available e.g. when even the formulation for adults has not been developed yet.</p>
Development of a particular pharmaceutical form	Development of <multiparticulate (granules)>, <film-coated tablets>, <very small tablets (minitablets)>, <dry powder in a single dose sachet>, < <i>i. v.</i> solution>, <oral liquid>, <oral solution>, <oral suspension>, etc.	<p>These requests are justified when the product is at an advanced stage of development, when most details about the active substance and various development scenarios have already been explored.</p> <p>Such request should be reflected in the opinion either when proposed by the applicant and agreed by the PDCO, or when proposed by the PDCO (and agreed by the applicant).</p>
Development of a particular strength	<p>Development of <xx mg film-coated tablets>, <yy mg/ml oral suspension>, <zz mg/ml oral solution>, <xx µg + yy µg per actuation, pMDI>, <xx µg + yy µg per actuation, DPI>, etc.</p> <p>or</p> <p>Development of a vial containing less than 10-fold of the lowest dose for adults</p>	<p>These requests are usually imposed when the dosing regimen is known.</p> <p>In order not to limit the applicant and bind to a particular strength, a range of strengths (e.g. 5 – 10 mg) can be used to define the flexibility level during development.</p>

Development of an alternative route of administration	Development of a pharmaceutical form for <intrathecal use>, <i.v. use>, <oral use>, etc.	
Development or inclusion of a medical device (administration device)	<p>A pre-filled pen <or other device, should be specified> which can deliver doses of <xx mg or xx – yy mg>, <specify the dose or the range>, must be made available for paediatric use.</p> <p>or</p> <p>To develop an appropriate measuring device allowing accurate dosing of small volumes (x to y ml) of the <liquid formulation>.</p> <p>or</p> <p>An oral syringe with suitable graduation should be added to the liquid formulation to be developed.</p> <p>or</p> <p>Development of an appropriate dispensing device for <film-coated very small tablets (minitablets)>, <granules>, <pellets>, etc.</p>	
Compatibility testing	To study the compatibility of <the active substance> with <specify the products (substances) to be tested with>	When requesting compatibility testing with other active substances (or medicinal products), these need to be specified in the request. Compatibility testing should be requested in situations when it is known that the product will be administered concomitantly (intensive care units, critically ill patients, situations where administration volume is critical, etc.). When requesting compatibility testing, a close collaboration with clinical experts is required to determine which active substances or medicinal products should be used. Although compatibility testing involves pharmaceutical evaluation, the need for such measure entirely depends on

	<p>or</p> <p>To study the compatibility/stability of <the active substance>, <pharmaceutical form> with common food and drinks.</p> <p>or</p> <p>A study on administration of <the active substance or the pharmaceutical form> via nasogastric tube. The dose recovery after extrusion through the feeding tube should be demonstrated using rinsing volumes relevant to the target population. In addition compatibility with the tube should be studied.</p>	<p>clinical aspects.</p> <p>Compatibility with food and drinks should be requested whenever it is foreseen that the product (substance) will be mixed with food or drinks (sprinkling granules or powder on food or mixing them with liquids, etc.).</p> <p>Whenever a product is to be administered via nasogastric tube, it should be demonstrated that this is feasible. Requests to use rinsing volumes relevant to the target population are important and should always be part of the key binding element.</p>
<p>Acceptability or palatability testing</p>	<p>The acceptability, including palatability, of <specify the dosage form, e.g. oral solution, oral suspension, etc.> should be confirmed during the clinical trial with the target population.</p> <p>or (if relevant)</p> <p>Acceptability of <specify the dosage form, e.g. tablets, capsules, etc.> should be tested during the clinical trial with the target population.</p>	<p>Whenever an oral liquid formulation is proposed, it is advisable to include a request for confirmation of acceptability of this formulation during a trial with the target population. In case of liquid formulations, acceptability includes palatability testing (taste, texture, flavour, etc.).</p> <p>In case of tablets, especially when proposed to the younger subsets of paediatric patients (6 – 8 years of age), or when the tablets size is large, their acceptability should be investigated and confirmed. Usually palatability testing for tablets is not needed.</p> <p>Due dates for acceptability (palatability) testing should be aligned with due dates for clinical studies during which the testing takes place. Having different deadlines may result in submission of the data as part of another application (due to compliance check rule).</p>

		Please note that when requesting acceptability (palatability) testing, a close collaboration with clinical experts is required, to ensure that the request is appropriately incorporated in the design of a clinical study. Although acceptability (palatability) testing relates to pharmaceutical aspects, its evaluation can only be performed as part of the clinical program.
Requests not to use (include) certain excipients in the formulation	<p>Preservative free <eye drops>, <oral liquid formulation>, <etc.> must be developed.</p> <p>or</p> <p>To replace <name the colouring agent, e.g. sunset yellow, etc.>, <name the sweetener, e.g. aspartame, etc.>, <name the solvent, e.g. ethanol, etc.> with another <colouring agent>, <sweetener>, <solvent> with better safety characteristics.</p> <p>or</p> <p>To remove <name the colouring agent, e.g. sunset yellow, etc.>, <name the sweetener, e.g. aspartame, etc.>, <name the solvent, e.g. ethanol, etc.> from the formulation.</p>	
Dilution/complex manipulation	To develop <a dosage form> <strength> which requires single dilution prior administration.	