Regulation (EC) No 726/2004

Art.	Par.	Original text	Revised Text	Comments
3	2	Any medicinal product not appearing in Annex I may be granted a marketing authorisation by the Union in accordance with this Regulation, if: (a) the medicinal product contains an active substance which, on 20 May 2004, was not authorised in the Union; or (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation ***or*** that the granting of authorisation in accordance with this Regulation is in the interest of patients' health at Union level.	Any medicinal product not appearing in Annex I may be granted a marketing authorisation by the Union in accordance with this Regulation, if: (c) the medicinal product contains an active substance which, on 20 May 2004, was not authorised in the Union; or (d) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation ***and*** that the granting of authorisation in accordance with this Regulation is in the interest of patients' health at Union level.	Consider addition of generics and nanomedicines to the list in Annex I.
6	1	Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. The documents must include a statement to the effect that clinical trials carried out outside the	Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. The documents must include a statement to the effect that clinical trials carried out outside the	Public funding received should be made transparent.

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Art.	Par.	Original text	Revised Text	Comments
		European Union meet the ethical requirements of Directive 2001/20/EC. These particulars and documents shall take account of the unique Union nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trade marks, shall include the use of a single name for the medicinal product. The application shall be accompanied by the fee payable to the Agency for the examination of the application.	European Union meet the ethical requirements of Directive 2001/20/EC. These particulars and documents shall take account of the unique Union nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trade marks, shall include the use of a single name for the medicinal product. The application shall be accompanied by the fee payable to the Agency for the examination of the application. ***Detailed written information on public funding received must be provided***.	
9	4cc	If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion: ***if appropriate,*** details of any recommended obligation to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the	If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion: ~~***if appropriate,***~~ details of any recommended obligation to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the	Detailed definition of specific criteria for efficacy studies.

Art.	Par.	Original text	Revised Text	Comments
		medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC.	medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC. ***Detailed information on ongoing studies (e.g. duration, outcomes, study type) to fulfil these obligations is to be published within a publicly accessible registry***.	
9	4	If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on: […] (e) the assessment report as regards the results of the pharmaceutical and pre-clinical tests and of the clinical trials, and as regards the risk management system and the pharmacovigilance system for the medicinal product concerned.	If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on: […] (e) the assessment report as regards the results of the pharmaceutical and pre-clinical tests and of the clinical trials, and as regards the risk management system and the pharmacovigilance system for the medicinal product concerned. ***Whenever a medicinal product is***	May apply simultaneously to the correspondent articles in the Directive.

Art.	Par.	Original text	Revised Text	Comments
			approved on the basis of a non-inferiority randomised controlled clinical trial, the assessment report should report on the excess of the absolute risk allowed as acceptable in the trial hypothesis.	
10a	1	After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study; (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate	After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study; (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate	Possibility to include criteria on when these studies have to be obligatory as well as a timeframe. Possibility to define legally binding reasons, under which EMA must require post-marketing studies– via delegated acts, see below Article 10b. Any post-launch requirements should be agreed with stakeholders.

Art.	Par.	Original text	Revised Text	Comments
		that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC. The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.	that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC. ***Obligations and specification as to the conduct of these studies have to be included within the JSC.*** The imposition of such an obligation shall be duly justified, notified in writing ***and published***, and shall include the objectives and timeframe for submission and conduct of the study. ***Any obligation shall be fulfilled within five years. If an obligation is not fulfilled in time or fails to resolve existing concerns relating to the efficacy or safety of the medicinal***	

Art.	Par.	Original text	Revised Text	Comments
			product, the marketing authorisation shall be revoked.	
10c	(new)		***After the granting of a marketing authorisation for a combination therapy, the new indication should be included in the approved therapeutic indication for all substances in the combination.*** ***The Agency shall inform all relevant marketing authorisation holders and provide an opportunity to present written objections in response to the decision within 30 days of receipt of the written notification of the decision.***	
12	1	The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product. Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect	The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product ***by means of randomised controlled clinical trials with an active comparator (unless this evidence could not be submitted due***	

Art.	Par.	Original text	Revised Text	Comments
		or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.	***to justifiable reasons which must be proven by the applicant)***. Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.	
13	4	After a marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised. The marketing authorisation holder shall notify the Agency if the product ceases to be placed on the market of a Member State, either temporarily or	After a marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised. ***In case of delays of actual marketing, the holder of the authorisation has to provide a justification. This information has to be published.*** The marketing authorisation holder shall notify the Agency if the product ceases to be placed on the market of a Member State, either temporarily or	Possibly within IRIS.

Art.	Par.	Original text	Revised Text	Comments
		permanently. Such notification shall, other than in exceptional circumstances, be made ***no less than two months*** before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the Agency of the reasons for such action in accordance with Article 14b.	permanently. Such notification shall, other than in exceptional circumstances, be made ***as early as possible but no less than two months*** before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the Agency of the reasons for such action in accordance with Article 14b.	
13	(new)		***If the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 10c of Directive 2001/83/EC. The Agency shall make this fact public.***	Possibility to apply this new provision only to marketing authorisation holders who have been granted rewards or incentives – if introduced, as currently provided in article 35 of the Paediatric Regulation 1901/2006.
14	3	Once renewed, the marketing authorisation shall be valid for an	Once renewed, the marketing authorisation shall be valid for an	

Art.	Par.	Original text	Revised Text	Comments
		unlimited period, unless the Commission decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.	unlimited period, unless the Commission decides, on justified grounds relating to pharmacovigilance ***or efficacy*** including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.	
14	4	Any authorisation which is not followed by the actual placing of the medicinal product for human use on the Union market within ***three*** years after authorisation shall cease to be valid.	Any authorisation ***according to article 14-a*** which is not followed by the actual placing of the medicinal product for human use on the Union market ***and by the submission of a P&R application in all Member States*** within ***two*** years after authorisation shall cease to be valid.	
14	5	When an authorised medicinal product previously placed on the market is no longer actually present on the market for ***three consecutive years***, the authorisation shall cease to be valid.	When an authorised medicinal product previously placed on the market is no longer actually present on the market for ***two consecutive years***, the authorisation shall cease to be valid.	
14	6	In exceptional circumstances and on public health grounds the Commission may grant exemptions	In exceptional circumstances and on public health grounds the Commission may grant exemptions from paragraphs 4 and 5. Such	

Art.	Par.	Original text	Revised Text	Comments
		from paragraphs 4 and 5. Such exemptions must be duly justified.	exemptions must be duly justified ***and the justification should be publicly available.***	
14	8	In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that ***he is unable*** to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.	In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that ***it is not possible*** to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.	CMA and authorisation under exceptional circumstances should only be possible via the centralised procedure and not anymore via the decentralised procedure or the MRP (hence, to be deleted from the Directive). The decentralised MA/mutual recognition should still be maintained for generics and for products for national needs.

Art.	Par.	Original text	Revised Text	Comments
14	(new)		***If a marketing authorisation under exceptional circumstances is subject to the specific obligation to complete an identified defined programme of studies, it shall be fulfilled within five years. If the specific obligation is not fulfilled in time or fails to resolve existing concerns relating to the efficacy or safety of the medicinal product, the marketing authorisation shall be revoked.*** ***The justification for a marketing authorisation under exceptional circumstances shall be published at the same time as the assessment report.***	See: • Ataluren (McDonald et al. 2017 doi: 10.1016/S0140-6736(17)31611-2) and • Pixantron (Pettengell et al. 2020 doi: 10.1111/bjh.16255) where this hasn't happened.
14	9	When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of ***therapeutic innovation***, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated.	When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of ***serving unmet medical and societal needs***, the applicant may request an accelerated assessment procedure. The request shall be duly	

Art.	Par.	Original text	Revised Text	Comments
			substantiated. ***The justification for an accelerated assessment must be published with the assessment report.***	
		If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(3), first subparagraph, shall be reduced to 150 days.	If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(3), first subparagraph, shall be reduced to 150 days.	
			If a medicinal product is authorised under this article, the MAH shall make the relevant data on treatment results and adverse reactions available to an independent indication-based registry set up by the EMA from the day of market entry.	For medicinal products that are authorised via the accelerated procedure resulting in conditional approval/approval under exceptional circumstances, data on treatment results and side effects (safety and efficacy) should be collected by the MAH from the time of market entry and fed into an independent indication-based registry at European level to enable the shared, comparative use of data for the evaluation of safety and comparative effectiveness.
14	11	Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an ***eight-year period of***	Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an ***six-year period of***	See also Article 10(1) and 24 of the Directive

Art.	Par.	Original text	Revised Text	Comments
		data protection and a ten-year period of marketing protection, in which connection ***the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications*** which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.	***data protection and a eight-year period of marketing protection***, in which connection ***the latter period shall be extended to a maximum of nine years if, during the first six years of those eight years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications*** which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.	
14-a	1	In duly justified cases, to meet unmet medical needs of patients, a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.	In duly justified cases, to meet unmet medical needs of patients, a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.	

Art.	Par.	Original text	Revised Text	Comments
		In emergency situations, a marketing authorisation for such medicinal products may be granted also where comprehensive pre-clinical or pharmaceutical data have not been supplied.	In emergency situations, a marketing authorisation for such medicinal products may be granted also where comprehensive pre-clinical or pharmaceutical data have not been supplied ***The justification for a conditional marketing authorisation must be published with the assessment report.***	
14-a	2	For the purposes of this Article, 'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.	For the purposes of this Article, 'unmet medical needs' means a ***life-threatening or seriously debilitating*** condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.	The essential UMNs are determined in a continuous process by a body/group (to be determined in more detail). Payer organisations must be included with seat and vote.
14-a	(new)		***The EMA, with the involvement of its Committees and all relevant stakeholders, shall establish a list of unmet medical needs as referred to in Article 14-a (2). The list shall be***	

Art.	Par.	Original text	Revised Text	Comments
			reviewed regularly and published in an electronically accessible form by means of an implementing decision of the European Commission.	
14-a	3	Marketing authorisations may be granted pursuant to this Article only if the risk-benefit balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data.	Marketing authorisations may be granted pursuant to this Article only if the risk-benefit balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data ***ideally by means of randomised controlled studies with an active comparator within the timeframe laid down in paragraph 4. Once these studies are available they have to be shared with the regulatory authorities and HTA bodies.***	
14-a	4	Marketing authorisations granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency.	Marketing authorisations granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified ***and published*** in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency. ***Any specific***	All data requirements (study designs, content, timeframe for submission) must be published and defined together with HTA/payer.

Art.	Par.	Original text	Revised Text	Comments
			obligation shall be fulfilled within five years.	
14-a	5	As part of the specific obligations referred to in paragraph 4, the holder of a marketing authorisation granted pursuant to this Article shall be required to complete ongoing studies, ***or to conduct new studies,*** with a view to confirming that the risk-benefit balance is favourable.	As part of the specific obligations referred to in paragraph 4, the holder of a marketing authorisation granted pursuant to this Article shall be required to complete ongoing studies ***or to conduct and complete new studies taking into due consideration the JSC,*** with a view to confirming that the risk-benefit balance is favourable. ***All studies must be published in the CTIS. Should the MAH deviate from the opinion given in the JSC, the reasons for doing so must be included and published within the EPAR***.	
14-a	(new)		***As part of the specific obligations referred to in paragraph 4, the holder of a marketing authorisation granted pursuant to this Article shall be required to market the product in all EU Member States.***	
14-a	8	When the specific obligations referred to in paragraph 4 of this Article have been fulfilled, the Commission may, following an application by the	When the specific obligations referred to in paragraph 4 of this Article have been fulfilled, the Commission may, following an application by the	

Art.	Par.	Original text	Revised Text	Comments
		marketing authorisation holder, and after receiving a favourable opinion from the Agency, grant a marketing authorisation valid for five years and renewable pursuant to Article 14(2) and (3).	marketing authorisation holder, and after receiving a favourable opinion from the Agency, grant a marketing authorisation valid for five years and renewable pursuant to Article 14(2) and (3). ***If a specific condition is not fulfilled in time or the marketing authorisation holder fails to resolve existing concerns relating to the efficacy or safety of the medicinal product by conducting the study according to 14(a)(5), the marketing authorisation shall be revoked.***	
16	3(a)	In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and ***promptly*** any such request.	In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and ~~***promptly***~~ ***without undue delay*** any such request.	
24	1	The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing	The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing	Registry for RWD should be added in order to take also effectiveness into account building on the experience from DARWIN EU.

Art.	Par.	Original text	Revised Text	Comments
		network (hereinafter the 'Eudravigilance database') to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.	network (hereinafter the 'Eudravigilance) to collate pharmacovigilance information ***as well as a RWD database to collate effectiveness information*** regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.	
57	1(a)	[The Agency shall provide the Member States and the institutions of the Union with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use or veterinary medicinal products which is referred to it in accordance with the Union legislation relating to medicinal products for human use or veterinary medicinal products. To that end, the Agency, acting particularly through its committees, shall carry out the following tasks:] coordinating the scientific evaluation of the quality, safety and efficacy of	[The Agency shall provide the Member States and the institutions of the Union with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use or veterinary medicinal products which is referred to it in accordance with the Union legislation relating to medicinal products for human use or veterinary medicinal products. To that end, the Agency, acting particularly through its committees, shall carry out the following tasks:] coordinating the scientific evaluation of the quality, safety and efficacy of	Studies must have the same structure („design") and be based on comparative evidence. This makes the studies comparable and facilitates the HTA processes; define further (in a delegated act) in a way that also HTA/P&R should be involved.

Art.	Par.	Original text	Revised Text	Comments
		medicinal products for human use and of veterinary medicinal products which are subject to Union marketing authorisation procedures;	medicinal products for human use and of veterinary medicinal products which are subject to Union marketing authorisation procedures; ***to this end, it formulates binding standards for uniformly designing the necessary scientific studies.***	
57	1(n)	advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use and of veterinary medicinal products;	advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use and of veterinary medicinal products; ***taking into account the requirements of Article 57 (1) a.***	See above
57	2	The database provided for in point (l) of paragraph 1 of this Article shall include the summaries of product characteristics, the package leaflet and the information shown on the labelling. That database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC. The database shall subsequently be	The database provided for in point (l) of paragraph 1 of this Article shall include the summaries of product characteristics, the package leaflet and the information shown on the labelling. That database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC. The database shall subsequently be	

Art.	Par.	Original text	Revised Text	Comments
		extended to include any medicinal product for human use authorised in the Union.	extended to include any medicinal product for human use authorised in the Union ***as well as the expiry of the respective regulatory and patent protection periods and SPCs.***	
83	3	When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency.	When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency ***and national reimbursement bodies***.	
83	4	When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, ***may adopt*** opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.	When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, ***adopts*** opinions on the conditions for use, the conditions for distribution and the patients targeted. ***The applicant must submit to the Agency all data necessary for the adoption of an opinion***. The opinions shall be updated on a regular basis.	
83	8	Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market.	Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market ***up to a national***	

Art.	Par.	Original text	Revised Text	Comments
			P&R decision. In case of a negative decision, the medicinal product should continue to be available free of charge.	
84a	6	Where the Commission finds that the marketing authorisation holder has failed, *intentionally or negligently*, to comply with its obligations, as referred to in paragraph 1, it ***may adopt*** a decision imposing a fine ***not exceeding*** 5 % of the marketing authorisation holder's Union turnover in the business year preceding the date of that decision. Where the marketing authorisation holder continues to fail to comply with its obligations referred to in paragraph 1, the Commission may adopt a decision imposing periodic penalty payments per day ***not exceeding*** 2,5 % of the marketing authorisation holder's average daily Union turnover in the business year preceding the date of that decision.	Where the Commission finds that the marketing authorisation holder has failed, *intentionally or negligently*, to comply with its obligations, as referred to in paragraph 1, it ***adopts*** a decision imposing a fine ***~~not exceeding~~ of at least ~~5~~ 3*** % of the marketing authorisation holder's Union turnover in the business year preceding the date of that decision. Where the marketing authorisation holder continues to fail to comply with its obligations referred to in paragraph 1, the Commission may adopt a decision imposing periodic penalty payments per day ***~~not exceeding 2,5 %~~ not less than 2 %*** of the marketing authorisation holder's average daily Union turnover in the business year preceding the date of that decision.	

Art.	Par.	Original text	Revised Text	Comments
		Periodic penalty payments may be imposed for a period running from the date of notification of the relevant Commission's decision until the failure to comply with the obligation by the marketing authorisation holder, as referred to in paragraph 1, has been brought to an end.		

Directive 2001/83/EC

Art.	Par.	Original text	Revised text	Comments
8	3 (new)		(cb) ***Evaluation of the appropriateness of the amount of active substance supplied in primary dosage form and packaging with regards to the intended use. The impact of inevitable waste shall be assessed and duly justified.***	Medicines are often not supplied in quantities that are appropriate for the intended use in patients. This results in waste that is a burden for both health care systems and with respect to cost and for the environment.
10	1	By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than ***eight*** years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until	By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than ***six*** years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until	

		ten years have elapsed from the initial authorisation of the reference product. […] The ***ten-year*** period referred to in the second subparagraph shall be extended to a maximum of ***eleven years*** if, during ***the first eight years of those ten years***, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.	***eight years*** have elapsed from the initial authorisation of the reference product […] The ***eight-year*** period referred to in the second subparagraph shall be extended to a maximum of ***nine years*** if, during ***the first six years of these eight years***, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.	
10	4	Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal	Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal	

		product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.	product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. ***These must allow for conclusions for all indications of the reference medicinal product.*** The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.	
10	5(a) (new)		***In addition to the provisions laid down in paragraph 1, an application for a new indication may be submitted by non-profit organisations with a particular interest in repurposing an authorised medicine for a new indication (« champions ») not holding a marketing authorisation themselves, if they have gathered or generated sufficient evidence to support a scientific rationale for their repurposing programme.***	

			Scientific advice shall be open for these champions and adding this indication to existing products should become a Type Ib application.	
10	6	Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.	Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements ***as well as preparatory regulatory steps, P&R applications and tender/procurement procedures on MS level*** shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.	
21a		In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions: […] The marketing authorisation shall lay down ***deadlines for the fulfilment of these conditions where necessary***.	In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions: […] The marketing authorisation shall lay down ***deadlines according to Article 22c(new) and criteria for the fulfilment of these conditions. The deadlines and conditions must be published.***	

22		***In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.*** ***The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.*** ***Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.***	***Delete***	The decentralised MA/mutual recognition should still be maintained for generics and for products for national needs.
22c	(new)		***Any condition referred to in Articles 21a, 22 or 22a shall be fulfilled within five years. If a condition is not***	See: • Ataluren (McDonald et al. 2017 doi: 10.1016/S0140-6736(17)31611-2) and

			fulfilled within five years or fails to resolve existing concerns relating to the efficacy or safety of the medicinal product, the marketing authorisation shall be revoked.	• Pixantron (Pettengell et al. 2020 doi: 10.1111/bjh.16255) where this hasn't happened
23	4	In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.	In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable ***and shall publish this data***. The marketing authorisation holder shall answer fully and promptly any such request. ***If this data is not transmitted within an established deadline after request of the national competent authority, the authorisation will be revoked.***	
23a		After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.	After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.	

		If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made ***no less than two months before*** the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2).	If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made ***no less than six months before*** the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2). ***If the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product on***	See also comment and amendment to Article 13 (new after 4), Regulation 726/2004) Proposal based on Art. 35, Regulation 1901/2006.

			the basis of Article 10c of Directive 2001/83/EC. The Agency shall make this fact public.	
		Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.	Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions. ***The competent authority shall publish this information on their website.***	
24	4	Any authorisation which within ***three years*** of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.	Any authorisation which within ***two years*** of its granting is not followed by the actual placing on the market ***and by the submission of a P&R application*** of the authorised product in the authorising MS shall cease to be valid.	
24	5	When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of ***three consecutive years***, the	When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of ***two consecutive years***, the	

		authorisation for that product shall cease to be valid.	authorisation for that product shall cease to be valid.	
26	1	The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared	The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant ***through randomised controlled clinical trials with an active comparator (unless this evidence could not be submitted due to justifiable reasons which must be proven by the applicant)*** or (c) its qualitative and quantitative composition is not declared	The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use.
29	2	Guidelines to be adopted by the Commission shall define a potential serious risk to public health.	Guidelines to be adopted ***and published*** by the Commission shall define a potential serious risk to public health.	
46	h	[The holder of a manufacturing authorization shall at least be obliged:]	[The holder of a manufacturing authorization shall at least be obliged:]	

		to verify that the manufacturers, importers or distributors from whom he obtains active substances are registered with the competent authority of the Member State in which they are established;	to verify ***towards the national competent authority*** that the manufacturers, importers or distributors from whom he obtains active substances are registered with the competent authority of the Member State in which they are established;	
46	i	to verify the authenticity and quality of the active substances and the excipients.	to verify ***towards the national competent authority*** the authenticity and quality of the active substances and the excipients.	
107b	1	Marketing authorisation holders shall submit to the Agency periodic safety update reports containing: (a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation; (b) a scientific evaluation of the risk-benefit balance of the medicinal product; (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing	Marketing authorisation holders shall submit to the Agency periodic safety update reports containing: (a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation; (b) a scientific evaluation of the risk-benefit balance of the medicinal product; (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing	Transparency as to the methodology and justification of scientific assessment and publication on the website.

		authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product. The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations. The periodic safety update reports shall be submitted electronically.	authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product. The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations. The periodic safety update reports shall be submitted electronically***, the national competent authorities shall publish this data/information including the methodology applied.***	
Annex I	Part I 5.1.	Reports of Efficacy and Safety Studies - Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication - Study Reports of Uncontrolled Clinical Studies - Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses	Reports of Efficacy and Safety Studies - Study Reports of (***Randomised)*** Controlled Clinical Studies Pertinent to the Claimed Indication - Study Reports of Uncontrolled Clinical Studies - Reports of Analyses of Data from More than One Study including any formal integrated analyses,	

		Other Study Reports	meta-analyses and bridging analyses Other Study Reports	
Annex I	Part I 5.2.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication In general, clinical trials shall be done as 'controlled clinical trials' ***if possible***, randomised ***and as appropriate versus placebo and*** versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; *thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo*.	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication In general, clinical trials shall be done as 'controlled clinical trials' ~~***if possible,***~~ randomised ~~***and as appropriate versus placebo and***~~ versus an established medicinal product of proven therapeutic value ***and only in justified individual cases in the absence of therapeutic alternatives a placebo can be used***; any other design shall be ***duly*** justified ***and the justification must be published***. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; ~~***thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.***~~"	

Annex I	Part I 5.2.5. 1(1)	***As far as* possible, and** particularly in trials where the effect of the product cannot be objectively measured, steps ***shall*** be taken to avoid bias, including methods of randomisation and blinding.	***~~As far as possible, and~~*** particularly in trials where the effect of the product cannot be objectively measured, steps ***must*** be taken to avoid bias, including methods of randomisation and blinding.	
Annex I	Part I 5.2.5. 1(2)	The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.	The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial. ***The study protocol of the trial as well as the statistical analysis plan must be published together with the marketing authorisation."***	
Annex I	Part II 4	[…] In case the originally authorised medicinal product has more than one	[…] In case the originally authorised medicinal product has more than one	The restriction to claimed indications leaves room for doubt, whether any indication not included is missing due to (a) patents, (b) a lack of interest by the MAH or

		indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the ***claimed*** indications.	indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the ~~***claimed***~~ indications.	(c) lack of similarity. This impedes regulation on interchangeability. Thus, similarity must be proven for all indications in the first run.
Annex I	Part II 6	DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES	Delete	Should only be part of the OMP Regulation or the Reg 726/2004
Annex I	Part III	ORPHAN MEDICINAL PRODUCTS	Delete	Update of the entire annex concerning Regulation 726/2004 as well as the OMP Regulation, e.g. OMPs are already covered by the Regulation and should not anymore be part of the Directive.