SUBMISSION OF COMMENTS ON STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE

Public consultation on legislative proposals

COMMENTS FROM: WYETH Pharmaceuticals
GENERAL COMMENTS

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 5, Section 3.2.4	*"ensure that the key risk management measures are included in the MA thereby ensuring that MAHs conduct the measures specified and provide updates to the CA and the EMEA as specified in the RMP"* We suggest that the process to achieve needs to be very clearly defined as it looks as if the RMP will need to be constantly reviewed by the MAH	
Page 6, Section 3.2.5	Codify oversight of non-interventional safety studies Wyeth is in agreement with the overall goal and rationale for the pharmacovigilance activities related to post-authorisation safety studies (PASS). The definition of non-interventional is not clear, and the proposed revised definition of a PASS is very broad (Article 1(15)). As written, almost all post authorisation studies could qualify as a PASS. The addition of *"characterising"* and *"or confirming the safety profile of the medicinal product"* are considered reasonable revisions to	

[1] Where available

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	this definition. However, it is unclear why *"in accordance with the terms of the marketing authorisation"* is intended to be replaced with *"with an authorised medicinal product"*. The conduct of a study using a product authorised in the EEA in accordance with the marketing authorisation (e.g. dose, indication) is a prerequisite to any post-authorisation study; the use of the term "with an authorised medicinal product" could be misinterpreted to suggest that a study using the authorised medicinal product, but in a different indication or using a different dose to that stated in the marketing authorisation, would qualify as a PASS. Consideration should be given to explicitly including in the definition that a PASS is primarily conducted to address a specific safety concern and/or with safety as the main objective. In addition, consideration should also be given to including that a study may also qualify as a PASS where the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s). In practical terms, this may be set as an arbitrary size (i.e. 1000 or more patients receiving the authorised product). Clarification is required as to the scope and nature of the "light oversight" of non-interventional post-authorisation safety studies (by EMEA pharmacovigilance committee only if conduct to be in more than one Member State). It should also be made clear whether the PASS requirements would also apply to non-interventional post-authorisation studies involving medicinal products authorised in the EEA being conducted solely outside the EEA.	
Page 7, Section 3.2.6	'*Medication errors that result in an adverse reaction should be reported to the competent authorities..."* We suggest that as currently these would <u>not</u> be reported if non serious that medication errors are re-classified as serious	
Page 7, section 3.2.6	*"The EMEA to take on new tasks, clearly defined in scope, for scanning of the scientific literature and entering case reports from the literature on Eudravigilance…*" We suggest that these cases also reach the MAH to enable them to enter the cases into their global safety database.	
Page 7, 2nd paragraph from the bottom of the page	We acknowledge the necessity to empower patients and to make it possible to self-report side-effects of their own medications. Most patients undergoing pharmacological therapy should hopefully also be able to notice a relief or a benefit ("response") to counterbalance experienced side-effects. However, for preventive therapies (e.g., vaccines) the situation is different. The benefit will not be immediately obvious to the vaccinated individual (or the parents of a vaccinated child) since it	

	consists of a future protection against disease (e.g. of infection). We are concerned that self-reporting of adverse events might lead to a significant accumulation of unrelated observations (cf. like frequent childhood infections) which might create a false perception of risk in general public. If, or when, a system of self-reporting (and parent reporting) is put in place, it will be crucial to ensure that these events are medically evaluated for relatedness before they are entered in the public domain of the database. While this applies to all medicines it is particularly relevant to preventive therapies. Due consideration has to be given by the legislator as to where and by whom the medical evaluation will be made.	
Page 8, section 3.2.6	*"changes on medication errors will benefit public health by ensuring that overdose and medication errors are reported to the relevant authorities with a clear legal basis"* We suggest that as currently these would not be reported if non serious that overdose is re-classified as serious	
Page 12, Annex 1, Article 1(15)	The revised definition of a PASS is very broad. As written, almost all post authorisation studies could qualify as a PASS. Furthermore the Current definition is only for "post-authorisation safety study, and not for "non-interventional post-authorisation safety study". The definition of "non-interventional post-authorisation safety study" should be clarified. This definition should also be in line with the current definition of the "non-interventional trial" as defined in the Directive 2001/20/Ec, article 2 (c), here below: *(c) non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;*	
Page 13, Annex 1, Article 11 (3)(b) {and also Article 59	"Key safety information" needs to be defined, as do the criteria for intensive safety monitoring	

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Page 20, Annex 1, Chapter 1, Article 101a	"*The Member States may impose specific requirements on doctors and other health-care professionals in respect of the reporting of suspected serious or unexpected adverse reactions*." Wyeth suggests removing the reference to reporting "serious or unexpected" reactions from the proposed wording in the legislation. Wyeth also suggests including reference to the European list of intensively monitored products referred to in Article 101j.	Therefore, consider the following revision to this paragraph: *"The Member States may impose specific requirements on doctors and other health -care professionals in respect of the reporting of suspected adverse reactions, including reporting for the European list of intensively monitored products referred to in Article 101j*."
Page 20, Annex 1, Chapter 1, Article 101a	*"Through the methods of collecting information and where necessary through the follow up of adverse reaction reports, the Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable."* Non-prescribed/dispensed medicines should also be subject to adverse reaction reporting.	Change to: *'any biological medicinal product prescribed, dispensed or sold in their territory which is the subject of an adverse reaction report …'*
Page 22, Annex 1, Chapter 4, section 1, article 101d	"*3. Individual adverse reaction reports held on the Eudravigilance database may be requested by the public and these data shall be provided by the Agency or the national competent authority from whom they were requested within 90-days unless this would compromise the anonymity of the subjects of the reports*." The Agency and national competent authorities should make clear in the relevant and appropriate implementing guidelines the type of information from individual adverse reaction reports within Eudravigilance that may be provided upon request to the public. Further, the information provided by either the Agency or the national competent authority(ies) should be standardised, taking into account applicable privacy laws and patient confidentiality, as well as giving consideration to the well documented limitations of data collected via spontaneous reporting and potential misinterpretations being made from this data. In addition, if the information provided relates to a specific product, the MAH should be informed that such information has been requested and provided.	

Page 22, Annex 1, Chapter 4, section 1, Article 101(e)1	*"Adverse reactions recorded shall be reports where the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility, and this shall include:* *(a) Reports where the Patient or the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; and* *(b) Reports where the Patient or the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown but the temporal relationship between the exposure to the medicinal product and the adverse reaction means that a causal relationship cannot be excluded."* Wyeth suggests clarifying how the patient is expected to assess a causal relationship. The suspicion of a causal relationship can be based on other reasons other than temporal relationship.	Suggest change to; *"Reports where the Patient or the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown but the ~~temporal relationship between the exposure to the medicinal product and the adverse reaction means that~~ MAH cannot exclude suspicion of a causal relationship ~~cannot be excluded~~."*
Page 22, Annex 1, Chapter 4, section 1, Article 101e, paragraph. 1	*"The marketing authorisation holder shall accept reports of adverse reactions electronically."* The use of the term 'electronically' can be confused with E2B reporting	Change to; *The marketing authorisation holder shal*l *implement the necessary mechanism to enable receipt of adverse reaction reports by electronic means*.
Page 23, Annex 1, Chapter 4, section 1, Article 101e, paragraph. 1.	"*These reports shall be collated at one point within the Community."* Clarification is requested on the need for these reports to be "collated at one point within the Community". The current requirement is for "all suspected adverse reactions…..collected and collated in order to be accessible at least at one point within the Community. " If the reports are required to now be collated at one point within the Community, this would be a significant impact on the organisational structure of pharmacovigilance systems.	
Page 23, Annex 1, Chapter 4, section 1, Article 101e. 2.	*"MA holders shall submit electronically to Eudravigilance, no later than 15-days following receipt of the report all the adverse reactions that occur in the community and all serious adverse reactions that occur outside the community. "* Wyeth suggest to clarify that 'the submission of all adverse reactions to Eudravigilance of all the adverse reactions that occur in the community' refers to non serious cases that are not currently reported	
Page 23, Annex 1,	*"Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15 -*	

Chapter 4, section 1, article 101e, Paragraph 2	*days following the receipt of the report, all adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community. "* The proposed wording implies that all adverse reactions (serious, non-serious, and medically unconfirmed reports) that occur in the Community will be subject to 15-day reporting to Eudravigilance. For the serious adverse reactions that occur outside the Community, the 15-day reporting to Eudravigilance is appropriate. Therefore, it is recommended to apply the 15-day reporting to Eudravigilance only to serious reports that occur in the Community, in accordance with Volume 9A. In addition, if non-serious reports that occur in the Community are required to be submitted to Eudravigilance, it should be taken into account that MAHs may allow longer timeframes for the processing of these non-expedited reports. Further, there is an apparent conflict with the requirements for submission of periodic ICSRs to Eudravigilance in Volume 9A, where submission of non-serious adverse reaction reports from worldwide sources are required to be submitted to Eudravigilance. In addition, if medically unconfirmed reports that occur in the Community are required to be submitted to Eudravigilance, this is contractory to the statement in current Volume 9A that medically unconfirmed adverse reactions should not be reported to the Agency/EudraVigilance on an expedited basis. Therefore, clarification is required.	
Page 23, annex 1, chapter 4, section 1, Article 101e, Paragraph 3	*« 3. The Member States shall record all adverse reactions that occur in their territory which are brought to their attention from healthcare professionals and patients."* For adverse reactions which are brought to the attention of the Member State by patients, appropriate case management, including the obtaining of medical confirmation of these adverse reaction reports, will need to take place, consistent with the responsibilities and tasks as laid down in CHAPTER 7, Article 101l. 2 (d): *"Operate a pharmacovigilance system to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings and evaluating such information scientifically"*	
Page 23, annex 1, chapter 4, section 1, Article 101e, Paragraph 3	*".....Member States shall submit electronically to Eudravigilance and to the marketing authorisation holders all of these reports which meet the notification criteria in accordance with the guidelines referred to in Article 101b."* Submission of these reports to Eudravigilance and to the MAHs should also be consistent with the	

	requirements laid down for the MAHs in Article 101e, paragraph 2.	
Page 23, Annex 1, chapter 4, Article 101e, Paragraph 3	"*The Member States shall ensure that reports of medication errors brought to their attention in the framework of adverse reaction reporting for medicinal products are made available to any national competent authorities for patient safety within that Member State. They shall also ensure that the national competent authorities for medicinal products are notified of any adverse reactions brought to the attention of national competent authorities for patient safety."* This requirement seems to imply that notification of any adverse reactions due to medication errors follows a different process other than reporting directly to EudraVigilance.	
Page 23, Annex 1, chapter 4, Article 101e, Paragraph 4.	« *By -/- (5-years after the entry into force of this directive), the Agency, in collaboration with the Member States shall make available web-based structured reporting forms for European healthcare professionals and patients to facilitate electronic reporting of adverse reactions and submission to EudraVigilance."* Does this mean patients and healthcare professionals will be able to report adverse reactions directly to EudraVigilance by these means? For adverse reactions which are reported by European healthcare professionals and patients using the web-based structured reporting forms, appropriate case management, including the obtaining of medical confirmation of patient adverse reaction reports, will need to take place for such reports.	
Page 23, Annex 1, chapter 4, Article 101(e) 5	*"The Agency shall monitor medical literature for reports of adverse reactions to medicinal products for human use authorized or registered in the Community. It shall publish the list of publications subject to this monitoring, and it shall enter into EudraVigilance relevant information from the identified literature."* It will be necessary to provide appropriate guidance to MAHs as to what will be the expectation with regard to their responsibility for scanning the scientific literature and potential submission to Eudravigilance. Such guidance will need to take into account the responsibilities of MAHs for branded medicinal products, as well as MAHs of generic medicinal products, to ensure that the appropriate scientific literature scanning continues to take place for all medicinal products authorised in the EEA. In addition, consideration will need to be given as to how the MAH is to be informed in a timely manner of the relevant information identified from the literature for their products, including ADR	

	information entered into EudraVigilance as individual case reports. Finally, guidance will be required on how the MAH can request publications to be added to the list of publications subject to this monitoring.	
Page 24, Annex 1, chapter 4, Article 101f, Paragraph 1	*"….Periodic safety update reports ……..not routinely contain listings of individual case reports already submitted to EudraVigilance."* In light of the EMEA's proposed scanning of scientific literature and entering of case reports on Eudravigilance, it is assumed that the MAH will not need to include a line listing of these same case reports from scientific literature in the PSUR	
Page 24, Annex 1, chapter 4, Article 101(f) 2c	The requirement to provide PSURs "immediately upon request" should take into account the time required to prepare PSURs which are requested outside the routine reporting cycle.	
Page 25, Annex 1, chapter 4, Article 101f, Paragraph 4(h).	"*The assessment conclusions shall be made public including any recommendations for the product information by the Agency via the European medicines safety web –portal referred to in Article 10 1i."* It may be reasonable to make public the assessment conclusions (but not the full PSUR assessment report) following adoption at the meetings of the Committee on Pharmacovigilance. Consideration should be given to utilising the current European Public Assessment Report (EPAR) process to communicate these assessment conclusions. The EPAR is intended to be updated throughout the authorisation period as changes to the original terms and conditions of the authorisation are made, and the assessment conclusions could be included in the EPAR for a medicinal product. Further, EPARs contain a summary written in a manner that is understandable to the public. This may warrant the extension of EPARs, or an equivalent, to medicinal products not authorised via the centralised procedure.	
Page 26, Annex 1, Chapter 4, Article 101 h (j)	"*In addition to any reporting requirements in the study protocol, the marketing authorisation holder shall submit an abstract of the study results to the Committee. The Committee may decide that the abstract is made public via the European medicines safety web -portal referred to in Article 10 1i or, after the agreement of the marketing authorisation holder, may decided that an amended abstract shall be made public."*	Suggest change to: "*In addition to any reporting requirements in the study protocol, the marketing authorisation holder shall submit an abstract of the study results*

	Agreement of the MA Holder should always be obtained for the publication of abstract, and not only for the publication of amended abstract.	*to the Committee. <u>After the agreement of the marketing authorisation holder,</u> The Committee may decide that the abstract is made public via the European medicines safety web -portal referred to in Article 10 1i or, ~~after the agreement of the marketing authorisation holder,~~ may decided that an amended abstract shall be made public."*
Page 26, Annex 1, Chapter 4, Article 101 h (j)	"*In addition to any reporting requirements in the study protocol, the marketing authorisation holder shall submit an abstract of the study results to the Committee. <u>The Committee may decide that the abstract is made public</u> via the European medicines safety web -portal referred to in Article 10 1i or, after the agreement of the marketing authorisation holder, may decided that an amended abstract shall be made public."* It is not clear whether the Competent authorities will have the same rights for single-country studies.	
Page 26, Annex 1, Chapter 4, Article 101 h (k)	*« Based on the results of studies the Committee may make recommendations for the product information and these shall be made public via the Agency web-portal."* The Committee should consult the marketing authorization holder before making its final recommendation publicly available.	Suggest to change to: *« Based on the results of studies <u>and after consultation of the marketing authorization holder</u>, the Committee may make recommendations for the product information and these shall be made public via the Agency web-portal."*
Page 28, Annex 1, Chapter 5, Article 101i, Paragraph 1.c	"*Information about how to report suspected adverse reactions to medicinal products and forms for their web-based reporting by patients, healthcare professionals and marketing authorisation holders*." The information, including adverse reactions reporting forms will be made available also to the MAH. Wyeth would suggest to clarify if this is in addition to reporting to EudraVigilance.	
Page 28, Annex 1, Chapter 5, Article 101i, Paragraph 1.d.	"*1. The Agency shall set up and update a European medicines safety web –portal in collaboration with the Member States and the Commission. By means of the European medicines safety web – portal, the Agency shall make public at least the following information:*	

	(d) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with Regulation (EC) No 726/2004." Consideration should be given to utilising the current European Public Assessment Report (EPAR) process to communicate the relevant information contained within risk management plans to the public. The EPAR is intended to be updated throughout the authorisation period as changes to the original terms and conditions of the authorisation are made, and relevant information contained within a risk management plan could be included in the EPAR for a medicinal product. Further, EPARs contain a summary written in a manner that is understandable to the public. This may warrant the extension of EPARs, or an equivalent, to medicinal products not authorised via the centralised procedure.	
Page 28, Annex 1, Chapter 5, Article 101i, Paragraph 1.(f).	"*1. The Agency shall set up and update a European medicines safety web –portal in collaboration with the Member States and the Commission. By means of the European medicines safety web – portal, the Agency shall make public at least the following information:* *f) A list of marketing authorisation holder qualified persons for pharmacovigilance and the Member State in which they reside."* The name and contact details of the qualified person responsible for pharmacovigilance are required to be notified to the competent authorities of the Member States and the Agency. The rationale for making public the details of qualified persons for pharmacovigilance is not clear – the qualified person acts as a single contact point for the Competent Authorities on a 24-hour basis for the competent authorities of the Member States and the Agency, and not the general public. Further, public release of the identities of qualified persons in a Member State may result in these individuals being targeted by protest groups.	
Page 28, Annex 1, Chapter 5, Article 101i, Paragraph 2.a.	*"2. Each Member State shall set up and update a national medicines safety web -portals which shall be linked to the European medicines safety web-portal referred to in paragraph 1. By means of the national medicines safety web -portals, the Member States shall make public at least the following information:* *(a) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with the procedures of this directive."* Consideration should be given to utilising the current European Public Assessment Report (EPAR)	

	process to communicate the relevant information contained within risk management plans to the public. The EPAR is intended to be updated throughout the authorisation period as changes to the original terms and conditions of the authorisation are made, and relevant information contained within a risk management plan could be included in the EPAR for a medicinal product. Further, EPARs contain a summary written in a manner that is understandable to the public. This may warrant the extension of EPARs, or an equivalent, to medicinal products not authorised via the centralised procedure.	
Page 32, Annex 1, Chapter 7, Article 101l. 2. c)	*"2. In addition to the general responsibilities as competent and supervisory authority and the specific responsibilities and tasks laid down in Articles 101a to 101k above, the Member States shall:* *c) If the qualified person for pharmacovigilance for a centrally authorised product resides in that Member State then the Member State shall act as the supervisory authority for pharmacovigilance inspections."* Consideration should be given to aligning the supervisory authority Member State for centrally authorised products to the MAH's pharmacovigilance system, and not necessarily to the country of residence of the qualified person. This would address potential scenarios where the qualified person's country of residence, country of work location, and the country where the main pharmacovigilance site/headquarters is located all differ. Instead, consideration should be given to permitting the supervisory authority Member State to be that in which the qualified person resides, *or* that Member State in which the pharmacovigilance system has it's main headquarters function. For pharmaceutical companies where the main headquarters function is located outside the EEA, the alternative would be the Member State in which the pharmacovigilance system has a central office within the EEA that has EEA-level pharmacovigilance responsibilities.	
Page 33, Annex 1, Chapter 7, Article 101l, Paragraph 4 (f).	"*Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices and place a report of the audit on the pharmacovigilance system master file."* These provisions require that reports of internal audits of an MAH's pharmacovigilance system shall be placed on the pharmacovigilance system master file which may be subject to inspection by competent authorities. It is not Wyeth company policy to provide audit reports to the authorities, since there is a need to protect audit reports so that they can provide a true and accurate picture of the situation that was the subject of the audit. If these are now required to be submitted to	

	authorities this may compromise the effectiveness of the audit process and undermine its usefulness as a compliance tool. It may, however, be reasonable to include details of a company's completed audit programme on the master file. In addition, the relevant audit certificates which certify that audits of pharmacovigilance tasks and processes have taken place may also be considered for inclusion.	
Page 39, Article 111 (8)	The reference to Article 101n should be 101o	
Page 39 - Articles 116 and 117 –	Removal of "under the authorised conditions of use": As written this indicates that regulatory action, including suspension, revocation or withdrawal of an MA may be taken if the risk/benefit is considered to be negative when the product is used outside the terms of the MA. These powers seem somewhat broad and the circumstances in which such action might be taken should be more clearly defined.	