15 June 2015

Dr Fergus Sweeney
Head, Inspections & Human Medicines Pharmacovigilance Division
European Medicines Agency
30 Churchill Place
Canary Wharf
London
E14 5EU

Dear Dr Sweeney,

We write on behalf of the European Federation for Exploratory Medicines Development (EUFEMED) and the European CRO Federation (EUCROF). This letter follows our recent stakeholder meeting on the transparency addendum for the EU portal and EU database, which took place at the EMA on 01 June 2015.

The purpose of the letter is to provide further information and evidence to support our position that the requirement to publish the (lay) summary of results 12 months after the end of a "Category 1" trial

(1) poses a risk to pharmaceutical sponsors' patents;
(2) does not meet the objectives and requirements of the new EU Clinical Trials Regulation.

(3) Therefore the requirement to publish Category 1 trials' summary results should be waived or delayed to a minimum of 24 months after the end of a trial.

We use the definition of Category 1 trials as proposed by the EMA during the stakeholder meeting:

- Phase I trials in healthy volunteers or patients to study pharmacokinetics, pharmacodynamics (and safety and tolerability)
- "Phase 0" trials
- Bioequivalence and bioavailability trials
- Similarity trials for biosimilar products, where a pharmacodynamic/efficacy endpoint is used to determine biosimilarity
- Equivalence trials for products where a pharmacodynamic/efficacy endpoint is used to determine equivalence (e.g. topical products)

(1) The requirement to publish the (lay) summary of results 12 months after the end of a Category 1 trial poses a risk to pharmaceutical sponsors' patents

Category 1 trials performed in Europe - and the results they generate - are used to support world-wide patent filings. Category 1 trials provide important information concerning the development of the medicinal product, e.g. indication(s), dosage(s), route(s) of administration, posology, pharmaceutical composition, use of excipients, pharmaceutical form(s) and formulation(s). Each of these features may form the basis for a patentable invention.

EUFEMED's and EUCROF's expertise in the area of patent law is limited. Our main contribution to the discussion around patent protection is information on the time it takes from the end of a trial to the reporting of results that may lead to results-based patent filing.

Straight-forward trials can be analysed and reported within a few months after "Last Subject Last Visit" (LSLV). The reporting of complex trials however require extensive bioanalytical and statistical analysis of biomarkers and other pharmacodynamic parameters. For these trials the timeline from LSLV to Clinical Study Report (CSR) encroaches on, or exceeds, 12 months after LSLV. Examples have been provided by a UK early phase research unit, where key pharmacokinetic, metabolism, and in one case biomarker data, required between 12 and 20 months post LSLV to be analysed and reported: EUDRACT N^{o}: 2012-003495-39; 2012-002137-10; 2013-001278-58; 2010-023295-40.

To provide further evidence, we collected and analysed data from Category 1 trials performed in two early phase clinical research units based in Belgium and in the UK. For the purpose of this analysis "end of trial" was defined as Last Subject Last Visit (LSLV); reporting of results was defined as the date of final Clinical Study Report (CSR). The latter definition was chosen because final results of trials must be available in order to file results-based patents. Only studies where a final CSR was available were taken into account for this analysis. A summary of the analysis is attached in the appendix to this letter. The underlying data can be provided on request.

Country	**Years**	**LSLV to CSR**
Belgium	2012 - 2014	Average time from LSLV to final CSR was around **11 months**
UK	2002 - 2014	The overall average time (days) between 2002 and 2014 from LSLV to final CSR was 301 days, approximately **10 months**
UK	2005 - 2008	90% of trials were reported within approximately **400 days**, i.e. within **just over one year** from LSLV
UK	2009 - 2011	90% of trials were reported within **502 to 749 days** from LSLV
UK	2012 - 2013	90% of trials were reported within **284 to 479 days** from LSLV

With the exception of years 2009 -2011 (UK data) the information gathered is consistent and suggests that **12 months** are an achievable *and* sustainable time frame **from LSLV to final CSR**.

Europe's strength in early phase clinical research is the capability to perform complex Category 1 trials:

- These trials require extensive analysis of pharmacodynamic/biomarker data after LSLV
- Sufficient time is required to report these trials
- Patents can only be filed after reporting has been completed

12 months from end of trial are clearly not enough to protect any innovation arising from these trials. Time must allow for the CSR to be finalised and a results-based patent to be filed prior to the publication of summary results. A 12-month window to publication of summary results would serve only approximately 50% of this sample of Category 1 trials (for data, see appendix), leaving a large proportion of sponsor companies exposed;

- This will be perceived as a significant risk to sponsors considering placing Category 1 work in Europe.
- Sponsors can choose from world-wide locations when placing their work; many will not wish to take this publication risk which is specific only to Europe.

(2) The requirement to publish the (lay) summary of results 12 months after the end of a Category 1 trial does not meet the objectives and requirements of the new EU Clinical Trials Regulation

After EUFEMED's recent conference in Brussels in May, the federation conducted a post-conference survey on the publication of summary results for clinical trials without therapeutic or prophylactic intent. EUFEMED conducted this survey following the pre-conference workshop "Implementation of the EU Clinical Trial Regulation – Opportunities and Threats to Early Medicines Development" and the open forum discussion on "New transparency rules in early phase non-therapeutic trials" during the main conference.

There were 94 responders; professionals with a background in academia, consultancy, contract research organisations, pharmaceutical industry and regulatory agencies. The full report is attached to this letter[(1)]. We summarise the main relevant outcomes below.

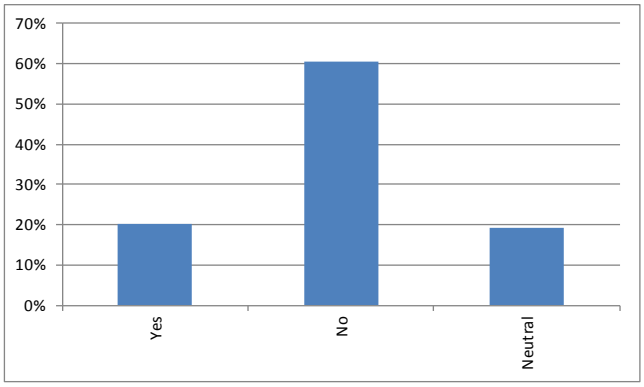
a. **Objective of the EU CTR to promote the benefits of transparency:**

Following a detailed risk/benefit assessment, we have written in previous submissions to the EMA that the publication of the (lay) summary of results 12 months after the end of Category 1 trials does not provide patients, healthcare professionals or the public with the benefits stated by ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the EU CTR.[(2)]

EUFEMED survey:
The EUFEMED survey confirms our previous assessment. 61% of responders' view is that the publication of summary results 12 months after the end of a "Category 1 trial" does not meet the objective to provide relevant information to patients, healthcare professionals and the public. Only 20% of the responders to the EUFEMED survey consider this publication beneficial to relevant stakeholders.

Survey Question:
With regards to academic and commercial clinical trials without therapeutic (or prophylactic) intent (Phase 0, Phase 1, BE and BA trials) and the requirement to publish their (lay) summary results 12 months after the end of the trial;

> "The information/data provided are relevant to patients, healthcare professionals and the general public; therefore their publication at that time is beneficial to these stakeholders"

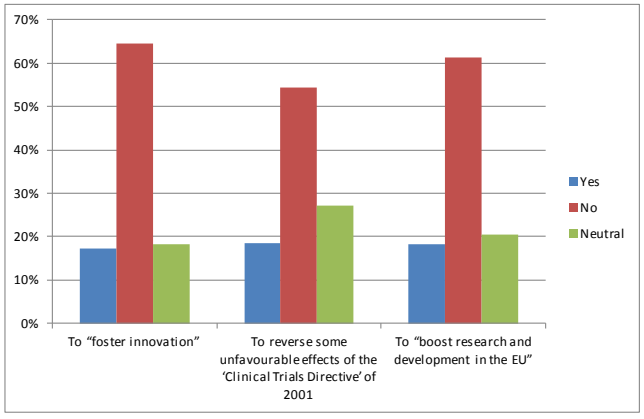


b. Objective of the EU CTR to promote innovation, research and development in Europe:

EUFEMED survey:
54 to 65% of responders stated that innovation, research and development in Europe will not be promoted by the publication of category 1 trial results 12 months after the end of a trial; Only 17 to 18% of survey responders stated that innovation, research and development in Europe will be promoted by the publication of category 1 trial results 12 months after the end of a trial.

Survey Question:
With regards to academic and commercial clinical trials without therapeutic (or prophylactic) intent (Phase 0, Phase 1, BE and BA trials) and the requirement to publish their (lay) summary results 12 months after the end of the trial;

> "The public availability of these summary results at that time meets the objectives of the new EU CTR"



c. Requirement of the EU CTR to recognize "the legitimate economic interests of sponsors" and to protect "commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure"

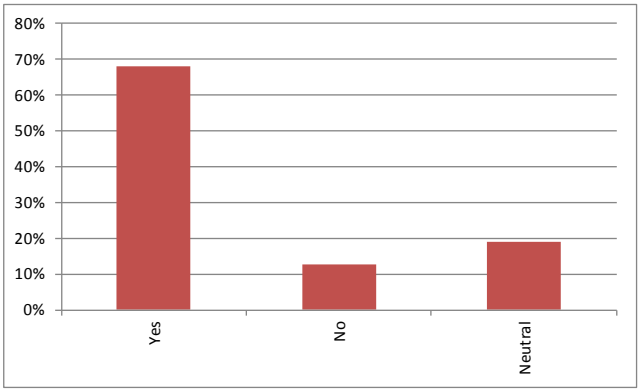
Our position is that, at 12 months after the end of a Category 1 trials, the information/data contained in their summary reports of results are commercially confidential *in their entirety*. The chemical/biological nature of the IMP together with information on potential indications, posology and trial methodology might be deduced from the disclosure of the data. Therefore:

- Disclosure requirements at that time infringe on sponsors' and investigators' rights to protect their innovations and potential patents.
- Disclosure requirement at that time will be perceived competitively disadvantageous by many sponsors and investigators conducting - or considering to conduct - Category 1 trials in Europe.

EUFEMED survey:
68% of survey responders stated that the requirement to publish at that time will have a significant negative impact on academic and commercial innovation and early phase drug development in Europe.

Survey Question:
With regards to academic and commercial clinical trials without therapeutic (or prophylactic) intent (Phase 0, Phase 1, BE and BA trials) and the requirement to publish their (lay) summary results 12 months after the end of the trial;

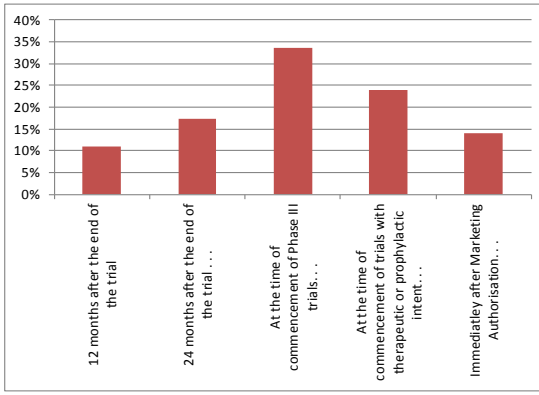
> "The information/data contained are commercially confidential and the requirement to publish at that time will have a significant negative impact on academic and commercial innovation and early phase drug development in Europe"



Whilst sponsors and investigators may wish to publish their Category 1 trials' summary results within 12 months after the end of a trial, they should not be forced to do so, in particular where there is no conceivable consequential benefit for patients, healthcare professionals and the public.

(3) The requirement to publish the (lay) summary of results 12 months after the end of a Category 1 trial should therefore be waived, or delayed to a minimum of 24 months after the end of a trial

When asked how the objectives of the new EU CTR would be best met, where publishing (lay) summary results is concerned, survey responders chose the following time-points after the end of a trial or in the drug development process:



Answer Choices	Responses	Percentage
12 months after the end of the trial	10	11%
24 months after the end of the trial (to allow sufficient time for patent filing)	16	17%
At the time of commencement of Phase III trials of the active substance and indication and formulation and route of administration under study	31	34%
At the time of commencement of trials with therapeutic or prophylactic intent of the active substance and indication and formulation and route of administration under study	22	24%
Immediatley after Marketing Authorisation of the active substance and indication and formulation and route of administration under study, or 10 years after the end of the trial, whichever is earlier	13	14%
Grand Total	92	

89% of responders chose 24 months after the end of a Category 1 trial as the earliest time for publication of summary reports; 48% of responders chose the commencement of Phase III trials - of the active substance, indication, formulation and route of administration of the IMP - as the earliest time for publication and as the best solution to meet all objectives and requirements of the CTR.

Summary:

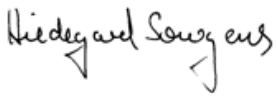
(1) 12 months after the end of a trial are not sufficient to protect innovations and patents arising from Category 1 trials.

(2) The requirement to publish Category 1 trials' summary results within 12 months after the end of a trial does not meet the objectives and requirements of the new EU Clinical Trials Regulation because:
   a. There is no conceivable benefit for patients, healthcare professionals and the public.
   b. The requirement to publish summary results at that time will be perceived as a significant risk by sponsors who consider placing Category 1 work in Europe.
   c. Sponsors can choose from world-wide locations when placing their work; many will decide against taking this risk, which is specific only to Europe.
   d. The disclosure requirement at that time infringes on sponsors' and investigators' rights to protect their innovations and potential patents.

(3) The requirement to publish of summary results of Category 1 trials should, due to the commercially confidential nature of those results, be waived or at the very minimum be delayed to 24 months after the end of a trial.

We thank you for considering our letter. Please do not hesitate to contact us, should you require any further information.

Yours sincerely,



Prof Hildegard Sourgens
President-Elect, European Federation for Exploratory Medicines Development

Dr Dagmar Chase
Vice-President EUCROF, Chair of EUCROF Clinical Trials Legislation Working Group

Dr Ulrike Lorch
Secretary, European Federation for Exploratory Medicines Development

Attachments:

(1) EUFEMED survey on publication of clinical trial results final report 10 June 2015
(2) EUCROF position paper Public Access to Early Phase EU database information 31 OCT 2014

Appendix: Time from Last Subject Last Visit to Final Clinical Study Report

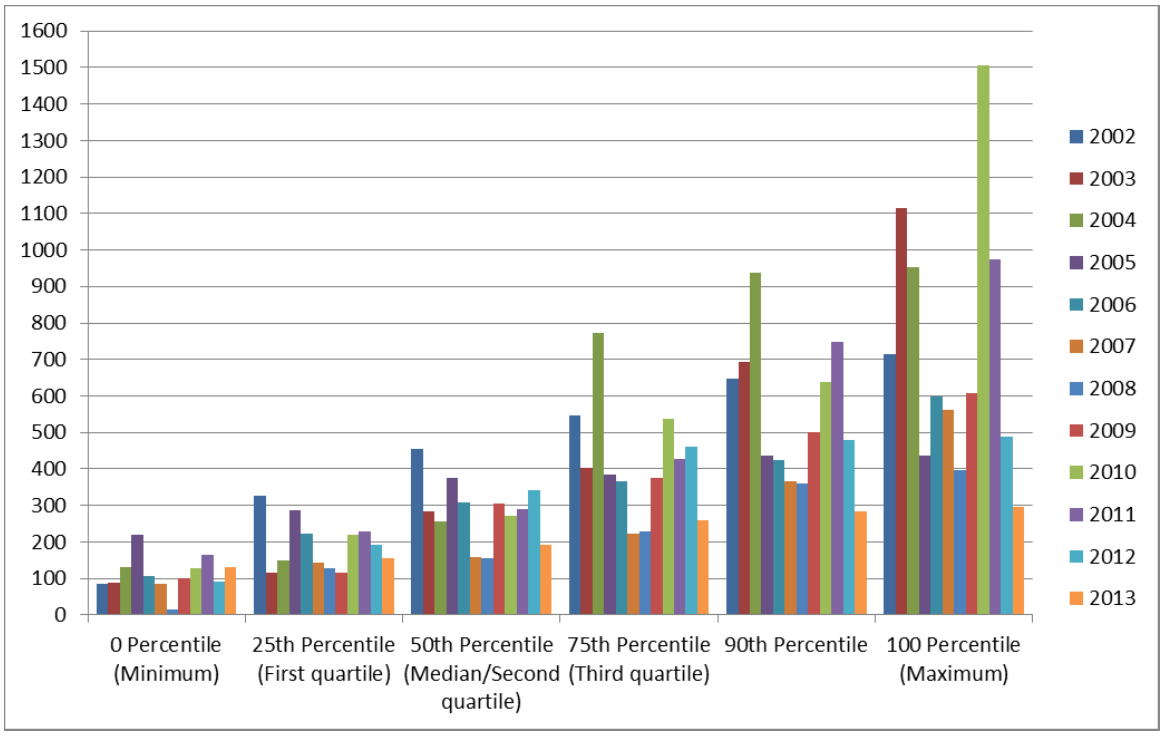
(1) Data from Belgium

Year CSR submitted	Number of studies	Time between LSLV and CSR final (months)	Minimum time (months)	Maximum time (months)
2012	34	10.9	8.1	11.9
2013	27	10.5	4.6	12.1
2014	32	11	8.2	11.5

(2) Data from UK

Average of LSLV - CSR	Ord														
Year STUDY END	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Grand Total
2002	85	326	714	546	455										425.2
2003	144	333	100	87	106	310	255	428	646	1116					352.5
2004	922	191	320	137	132	953									442.5
2005	287	250	377	219	369	435	437	375	386						348.3333333
2006	366	249	368	285	329	213	600	405	107	130					305.2
2007	144	140	561	367	144	181	84	351	171	155	160	137			216.25
2008	151	372	144	127	329	160	185	131	397	15	95	126	199	238	190.6428571
2009	430	321	127	305	609	101	105								285.4285714
2010	127	242	273	463	1507	130	610	259	274	639	198				429.2727273
2011	329	231	227	165	352	975	250	652							397.625
2012	490	453	91	228											315.5
2013	158	152	258	296	287	131	132	168	258	176	220	206			203.5
2014	277	92	143	148	187	123									161.6666667
Grand Total	300.8	257.8	284.8	259.5	400.5	337.5	295.3	346.1	319.9	371.8	168.3	156.3	199	238	301.1578947

	0 Percentile (Minimum)	25th Percentile (First quartile)	50th Percentile (Median/Second quartile)	75th Percentile (Third quartile)	90th Percentile	100 Percentile (Maximum)
2002	85	326	455	546	646.8	714
2003	87	115.5	282.5	404.25	693	1116
2004	132	150.5	255.5	771.5	937.5	953
2005	219	287	375	386	435.4	437
2006	107	222	307	367.5	424.5	600
2007	84	143	157.5	223.5	365.4	561
2008	15	128	155.5	228.25	359.1	397
2009	101	116	305	375.5	501.6	609
2010	127	220	273	536.5	639	1507
2011	165	230	289.5	427	748.9	975
2012	91	193.75	340.5	462.25	478.9	490
2013	131	156.5	191	258	284.1	296
2014	92	128	145.5	177.25	232	277



2014 excluded from graph/final analysis as for a number of trials completed CSR still outstanding