5 August 2013
EMA/443893/2013
Human Medicines Development and Evaluation Special Areas

Comments from the public consultation on the revised priority list of off-patent medicines for children 2013/14

Comments from

	Name of Organisation or individual
1	Instituto de Investigación Biotecnológica, Farmacéutica y Medicamentos Huérfanos, S.L.; Almudena Gómez, 18016 Granada, Spain
2	Dr Grenville Fox, Consultant Neonatologist, Gu's & St.Thomas NHS Foundation Trust, London
3	Medicines for Children Research Network, The Netherlands
4	European Paediatric Gastroenterology, Hepatology and Nutrition Clinical Trials Network (ESPGHAN, BSG, ISG, DSG, ENPR-EMA) Submitted by the project lead Dr Nicholas Croft
5	Liverpool Women's NHS Foundation Trust

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

	Name of Organisation or individual
	(Dr. Mark Turner, Director of Research and Development)
6	UK Paediatric Gastroenterology, Hepatology and Nutrition Clinical Studies Group (Medicines for Children's Research Network, British Society of Paediatric Gastroenterology, Hepatology and Nutrition) Submitted by the Co-Chair Dr Julian Thomas

Please note that these comments and the identity of the sender will be published unless a justified objection is received.

Comments should be sent to the EMEA electronically and in word-format (not pdf) only using this template.

Comments on the revised priority list

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
General			
4	General	It is not clear what range of drugs this should cover in particular drugs coming off patent in the near future. Should these be considered at all or when will this list next be refreshed and allow newly off patent drugs to be considered?	The list which is revised on an annual basis should only cover off-patent products.
5	General	We welcome this opportunity to contribute to development of the priority list	The PDCO acknowledged this comment.
Cardiology			
2	To add: sildenafil	Add Sildenafil to list for treatment of pulmonary hypertension associated with bronchopulmonary dysplasia in preterm / ex-preterm infants	The PDCO did not consider this as a priority as there is an agreed Paediatric Investigation Plan (PIP) for this product/condition.¶
3	To add: sildenafil	Sildenafil in pulmonary hypertension; data on PK,PD, safety, efficacy and age appropriate formulation *(also neonatology and ICU)*	The PDCO did not consider this as a priority as there is an agreed Paediatric Investigation Plan (PIP) for this product/condition. ¶
3	To add: milrinone	Milrinone for circulatory enhancement in ICU setting; data on PK,PD, safety, efficacy and age appropriate formulation	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
3	To add: spironolactone	Aldosteron antagonist (Spironolacton) in (impending)heart failure; data on PK,PD, safety, efficacy and age appropriate formulation	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided.
4	Propranolol (p3)	Comment: Also need to add use in portal hypertension as there is a bad need for studies in this area: PK/PD, efficacy and safety Proposed change (if any): Add the above indication for study of propranolol	The PDCO did not consider this as a priority as further scientific justification needs to be provided. It will be considered for further discussion with experts and inclusion in the Paediatric Inventory.*

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
6	Propranolol	Comment: Also to add use in portal hypertension PK, efficacy and safety	As above.
1	Enalapril	We were developing a project with Enalapril for the treatment of cardiac problems. I have seen that you have published the *Revised provisional priority list for studies into off-patent paediatric medicinal products* in your website on June 5. In the previous list it was included Enalapril, but in the updated one it has been removed. I have looked for Enalapril in the PIP applications, and there is no PIP for this product, and also I have tried to look for Enalapril in the Horizon 2020 list but I have not found any conclusion. Is there any reason to exclude this product or could we continue with our project?	The 7th call of FP7 has led to the selection of a proposal dealing with the use of enalapril from neonates up to adolescents. Therefore this product had to be taken off the priority list.
3	To add: bosentan	Bosentan: < 2 years, (also neonatology and ICU), data on PK,PD, safety, efficacy and age appropriate formulation	The PDCO did not consider this as a priority as there is an agreed Paediatric Investigation Plan (PIP) for this product/condition. ¶
Dermatology			
3	To add: propranolol	Propranolol for haemangioma	The PDCO did not consider this as a priority as there is an agreed Paediatric Investigation Plan (PIP) for this product/condition. ¶
Endocrinology			
3	Metformine	Metformine in T2DM < 10 years	The PDCO did not consider this as a priority.
Gastroenterology			
3	To add: azathioprine	Azathioprine: Crohn's disease: Data on efficacy and safety vs placebo in mild CD; Data on efficacy and safety vs methotrexate in moderate to severe CD. Ulcerative colitis: Data on efficacy and safety vs placebo in moderate to severe UC	The PDCO included the following in the off-patent priority list: "Data on efficacy and safety alone or in combination with biological; age-appropriate formulation."
4	Azathioprine (p4)	What is the efficacy in mild – moderate Crohn's disease and its role in maintenance of remission when remission has been induced by nutritional	As above.

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
		therapy. There has been only one good quality study clearly showing benefit (of 6-MP) and this was using steroids to induce remission. Nutritional therapy is generally felt to be better at producing mucosal healing than steroids and so medium to long term outcome may be different.	
6	For Azathioprine	What is the efficacy in mild – moderate Crohn's disease and its role in maintenance of remission when remission has been induced by nutritional therapy. There is only one good quality study showing benefit of 6-MP and this was using steroids to induce remission.	As above.
3	To add: MTX (GASTROENTEROLOGY)	MTX: MTX sc vs oral	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided.
3	To add: infliximab	After Feb 2015: infliximab: data on efficacy and safety of infliximab vs humira and of these products vs biosimilars	The PDCO did not consider this as a priority as this product still seems to be patent-protected.
4	To add: domperidone	Advise domperidone be added to the priority list. This is widely used in the treatment of reflux in infants with a rational scientific basis for possible benefit but with no good quality studies. PK, PD, efficacy and safety	The PDCO did not consider this as a priority as this product is under review for safety issues.
6	To add: domperidone	Advise domperidone be added to the priority list.	As above.

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
		This is widely used in the treatment of reflux in infants with a rationale basis for possible benefit but with no good quality studies. PK, PD, efficacy	
4	To add: sennakot	Page 3 – Bisacodyl is included but would advise Sennakot also included. There is very little in the way of good data of the benefits of stimulant laxatives in addition to osmotic laxatives in childhood constipation.	The PDCO did not consider this as a priority as sennosides are authorised in Europe (e.g. in the UK) from the age of 2 years onwards. It will be further discussed and considered for the inclusion in the Paediatric Inventory.*
6	To add: sennakot	Page 3 – Bisacodyl is included but would advise Sennakot also be considered. The there is very little in the way of good data of the benefits of stimulant laxatives in addition to osmotic laxatives in childhood constipation.	As above.
4	P3 Omeprazole Ulcer prophylaxis in intensive care unit (ICU) patients	The indication is very specific. Propose a broader theme e.g. 'Ulcer prophylaxis' To include ICU patients, patients using steroids, NSAIDS. Data on PK, safety, efficacy for IV and oral use	The PDCO included the following condition in the off-patent priority list: "Ulcer prophylaxis in patients at risk (e.g. intensive care unit, treatment with corticosteroids)"
6	Omeprazole (p3)	the indication is very specific. Although interesting I would be more keen for a broader theme e.g. ulcer prophylaxis e.g. ICU patients, patients using steroids, NSAIDS. Data on PK, safety, efficacy for IV and gastric use	As above.
4	Mesalazine (p3)	Need to include efficacy and PK of age appropriate once day preparations	The PDCO concluded not to change the existing wording as it already covers the comment.

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
4	Mesalazine (p3)	Include both small bowel and colonic Crohns in addition to UC. This is widely used but there is little or no good evidence and data is badly needed to demonstrate if any efficacy and benefit for the patient. Efficacy and safety	The PDCO included the following condition in the off-patent priority list: "Inflammatory bowel disease"
6	Mesalazine	broaden UC to 'inflammatory bowel conditions' e.g. ulcerative colitis, food allergic/eosinophilic colitis. Keep the data on efficacy and safety compared to suphasalzine	As above.
6	Ursodeoxycholic acid	Is it possible to add the use of Ursodeoxycholic acid in liver diseases – (1) liver associated pruritis (2) sclerosing cholangitis and (3) CF associated liver disease PK, efficacy and safety data	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
6	penicillamine, zinc acetate, trientine M Wilson	Treatment of Wilson Disease Suggest adding penicillamine, zinc acetate, trientine	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided.
6	To add: rituximab	Treatment of refractory Auto immune liver Disease Proposed change (if any): Add biologicals, particularly rituximab	The PDCO did not consider this as a priority as this product still seems to be patent-protected.
6	Ciclosporin (p4)	Conditions: Add the use of ciclosporin in acute severe colitis. A recent high quality paper in adults suggests this is the equivalent of biologics, there have been no good studies in children.	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
Immunology			
6	Immunology section Azathioprine	Comment: also to add use in autoimmune liver disease (data on PK, safety and efficacy	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
6	Azathioprine, ciclosporin, methotrexate	A major issue for these with no useful data in is the lack of information regarding vaccine efficacy and this topic should be added.	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
Infections			
6	To add: Anti-virals against HBV, Entecavir, Adofovir, Tenofovir, Telbivudine and for HCV boceprevir and telaprevir	Anti-virals against HBV, HCV need to be added Proposed change (if any): Add Entecavir, Adofovir, Tenofovir, Telbivudine and for HCV boceprevir and telaprevir	The PDCO did not consider this as a priority as there are agreed Paediatric Investigation Plans (PIP) for this products/conditions¶ (Tenofovir: Human immunodeficiency virus (HIV) disease resulting in other conditions Chronic viral hepatitis B; Entecavir: Treatment of chronic hepatitis B; Boceprevir: Treatment of chronic hepatitis C; Telaprevir: Treatment of chronic viral hepatitis C)
Intensive care / Anaesthesiology			
3	To add: propofol	Propofol for anaesthesia	The PDCO considers this product as a priority for the condition “short-term sedation for procedures” which is already included.
3	To add: sufentanil	Sufentanil: data on PK,PD, safety, efficacy	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided.
3	To add: fentanyl	Fentanyl < 2 years	The PDCO did not consider this as a priority as there is an agreed Paediatric Investigation Plan (PIP) for this product/condition. ¶

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
3	To add: bupivacaine	Bupivacaine < 1 years	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
3	To add: ropivacaine	Ropivacaine for local infiltration and peripheral nerve block	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
Neonatology			
5	spironolactone	Comment: Spironolactone is not used as monotherapy for bronchopulmonary dysplasia. The research about diuretics in chronic lung disease investigates thiazides or loop diuretics. Some, but not all of these studies include spironolactone as a potassium-sparing diuretic. According to the Cochrane reviews on diuretics in bronchopulmonary dysplasia, the thiazide diuretics have been most widely studied. Of these, data for chlorothiazide provides the strongest evidence for proof-of-concept. Furosemide has a more severe adverse event profile than the thiazides. While intravenous furosemide may have a role in the initiation of diuretic therapy for bronchopulmonary dysplasia, an oral preparation will be needed for long-term treatment. Proposed change (if any): Add a new row: stating chlorothiazide as treatment for bronchopulmonary dysplasia, with or without spironolactone. Data on	The PDCO agreed with this comment and amended the list accordingly with the following wording: Chlorothiazide for treatment of Bronchopulmonary Dysplasia with the priority on data on PK, efficacy and safety alone or in combination with spironolactone; age-appropriate formulation.

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
		safety, efficacy, PK and age-appropriate formulation. Comment: The indications for spironolactone listed (bronchopulmonary dysplasia, ascites, oedema) are diverse. Proposed change (if any): Remove mention of oedema and ascites from the row relating to bronchopulmonary dysplasia.	
Nephrology			
3	To add: furosemide	Furosemide for diuresis, data on PK,PD, safety, efficacy	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. Furthermore it is authorised in Europe (e.g. UK) in the paediatric population.
Neurology			
3	To add: levetiracetam	Levetiracetam for epilepsy syndromes; efficacy and safety < 16 years	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory.*
Pain			
3	To add: diclofenac	Diclofenac for acute pain	The PDCO did not consider this as a priority as this product is under review for safety issues.
3	To add: paracetamol	Paracetamol IV < 1 years	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. The product is authorised in Europe (e.g. UK) for children with a body weight below 10 kg.

Stakeholder No. <*to be completed by EMA*>	Name of product	Comment/Scientific justification	Outcome PDCO
Pneumology			
3	To add: Long acting beta agonists (salmeterol, formoterol)	Long acting beta agonists (salmeterol, formoterol) in asthma, young children; efficacy and safety	The PDCO did not consider this as a priority as scientific justification/rationale needs to be provided. It will be considered for the inclusion in the Paediatric Inventory* for children below the age of 4 years.
3	To add: Long acting anticholinergics (tiotropium)	Long acting anticholinergics (tiotropium) in asthma, young children; efficacy and safety	The PDCO did not consider this as a priority as this product still seems to be patent-protected. There is an agreed Paediatric Investigation Plan (PIP) for this product. ¶

¶ Information on opinions and decisions on paediatric investigation plans is published on the EMA website.
* Further information on the Inventory of Paediatric Needs can be found on the EMA website.