make medicines child size

Paediatric Regulators Network Meeting

Geneva, 15-17 February 2010

Report to WHO concerning international guidelines for paediatric medicines

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1. Executive summary

It is well recognised that medicines suitable for children are not as readily available as those for adults, especially adults in the economically developed world. Manufacturers have little commercial incentive to develop and make available paediatric medicines, or to improve the limited evidence base that might inform selection of drug, dosage form and strength for paediatric indications. The costs and risks of research are significant, especially given that returns are likely to be lower than in other areas to which the same resources might be committed.

Governments can provide financial and legal incentives to change this situation, and regulatory authorities can provide advice that might give manufacturers the confidence that their investment in product development will be rewarded. Regulatory guidelines are the means by which authorities disseminate the scientific advice that manufacturers can rely upon. The guidelines must be sufficiently authoritative that regulators cannot dismiss applications based upon them without good cause, provided of course that the methodology and results are sound.

The objective of this review was to survey the legislation and guidelines published by medicines regulatory authorities that might give manufacturers both incentives and the confidence to invest in development of paediatric medicines.

The third term of reference for this report reads:

> *"To give an expert opinion if there are any major gaps in the set of guidelines existing globally that could help manufacturers in creating paediatric formulations".*

This ToR asks what regulatory guidelines might encourage development of paediatric medicines. In interpreting what is meant in this context by *regulatory guidelines,* it is noted that most guidelines (or *guidances* in the USA) that are issued by regulators are advisory rather than prescriptive and it is open to applicants to offer alternative means of supporting an application. In contrast legislation is prescriptive and unalterable except by legal appeal. This term of reference has been interpreted as including consultative publications such as the EU *Reflection paper: Formulations of choice for the paediatric population* and *Concept papers*.

Searches revealed that many regulatory authorities have little in the way of registration guidelines for any forms of medicine. However many websites cross-referred to international guidelines, such as those of ICH, FDA and the EMA, and this is a welcome means of facilitating product development by reducing the number of hurdles that must be crossed to achieve multinational registration.

Section 5 of the report suggests what additional measures might help manufacturers in developing paediatric medicines. This author is not qualified to give an opinion concerning preclinical and clinical guidelines.

At a country level, the UK approach of defining strategies for short, medium and long term application may be useful. See the details in Table 6 below. Appropriate dedicated, supporting infrastructure should be a part of any such strategy.

2. Terms of reference

1. To trace down, list and review all the existing regulatory requirements/technical guidelines specific to paediatric medicines both in well resourced (ICH regions including also ICH associated countries such as Switzerland, Canada and Australia) and less resourced settings (countries like China, India, Brazil and Russia deserve specific attention in this respect).
2. To describe shortly (maximum half a page) the content of each regulatory guideline.
3. To give an expert opinion if there are any major gaps in the set of guidelines existing globally that could help manufacturers in creating paediatric formulations.
4. To present a written report about the results of the review.

3. Search strategy

WHO has prepared a list of web addresses for regulatory authorities[1]. All were searched for documents relevant to registration of paediatric medicines. Each site that could be accessed was searched for *paed*, *pedi* and *child*, both directly and via the *in URL* search function. Those websites in Spanish but not in English were searched for *nino*, *niño*, *paed* and *pedi*.

Where no documents were found with *paed*, *pedi* or *child* in the title, general guidelines relating to registration of medicines were searched for references to *paed*, *pedi* or *child*. Only significant references were recorded, excluding for example a requirement that recommendations for paediatric dosing must specify an age range.

When no relevant references were found on a website, email enquiries were pursued if the agency was in a country explicitly mentioned in the terms of reference. As far as possible, the website *contact us* or similar function was used, as well as personal contacts. As a last resort the WHO regional office was asked to assist.

The websites mentioned in the Terms of Reference were searched thoroughly. Available summary publications were used as sources as far as they were relevant [2-4].

4. Results and summaries

The results of the review are presented in five sections:

- Notes after searching each of the regulatory websites identified by WHO.
- Documents retrieved for Europe.
- Documents retrieved for the USA.
- Documents retrieved for WHO.

- Other relevant documents, sorted according to country of origin.

In the tables that contain summaries of documents, no entry was made in the summary/notes column when the content was self-evident in the document's title.

For formatting reasons, URLs are provided as footnotes to the tables. These can be cut and pasted into an internet browser to download the document. In Word 2007, control click will open the URL.

Individual documents are referenced in this report by table number, and row number as defined in the first column. For example Table 4 Row 4 is the *Pediatric Research Equity Act*.

International documentation uses both of the spellings *paediatric* and *pediatric*. These words are interchangeable and there is no difference in meaning.

4.1 Searches of regulatory websites

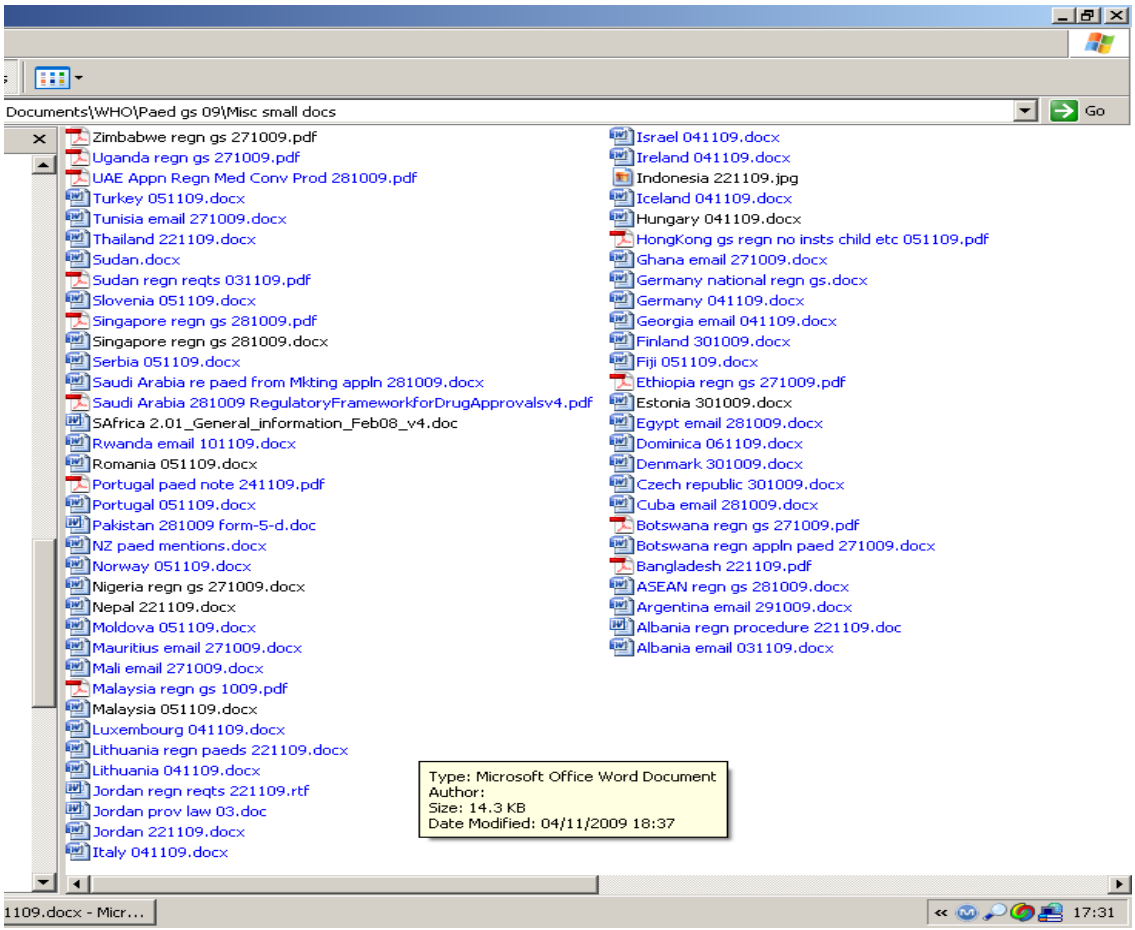
WHO's list comprised 193 countries, for which 120 websites had been identified [1] (see Table 2). Several sites could not be located or could not be accessed or did not have an English language option. Where the table states that an email has been sent but does not mention a reply, then no reply has been received as of the date of finalization of this report.

Table 1 below summarizes results of the review. Table 2 below lists relevant documents that were found and summarizes the content of each.

Table 1 Summary of searches regulatory websites

Macro outcome	
Total websites identified by WHO.	120
WHO advises that no website exists	75
Sum	*195*
Detailed findings	
An entry was made in one of Tables 4 to 6 below	6
No relevant and significant documents found. Includes 7 x 'website under construction' or similar.	80
Did not find an English section of the website	30
Could not open the website	4
Sum	120

For some countries a file or folder was created to store the information that had been retrieved. A list of these follows. In the author's opinion none deserves a discussion in this report. Copies may nevertheless be obtained from susanw@netspeed.com.au.



4.2 Documents retrieved for Europe

Table 3 lists relevant documents located for Europe[1] and provides a summary of each. The table is sorted into legislation, concept papers & guidelines/resources, and then by date.

When reviewing the EMEA website, note that:

- EMEA publishes *Concept papers* that outline future plans. Several of these relate to paediatric guidelines, and are included in Table 3.
- Some of the guidelines relating to paediatric medicines are located in the multidisciplinary part of the site, and others under the heading of efficacy.

A short paper entitled The European paediatric initiative (Row 16 in Table 3) provides a history of the European Paediatric Regulation and its implementation. The current regulatory situation is best summarized in *Better medicines for children* (Row 23 in Table 3).

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1 The European Agency for the Evaluation of Medicinal Products (EMEA) has changed its name to the European Medicines Agency (EMA). However documentation is inconsistent in the use of the two terms. Better medicines for children (Row 23 Table 1.3) illustrates use of both names & abbreviations, apparently interchangeably.

A regulation concerning *medicinal products for paediatric use* was adopted by the European Commission in December 2006 (see Row 1 in Table 3) A second regulation (Row 2) made minor amendments. Together these are referred to as the *Paediatric Regulation*. Stated objectives are (Row 23 Table 3):

- "facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately, and
- improving the availability of information on the use of medicines for children,

without:

- subjecting children to unnecessary trials, or
- delaying the authorization of medicinal products for use in adults".

In summary for Europe:

- From July 2008, applications for marketing authorization must include the results of studies conducted in the paediatric population as per the *Paediatric investigation plan* (PIP) with the exception of:
  - Generics
  - 'Similar' biological medicinal products
  - Medicinal products authorized via the well-established medicinal use procedure[2]
  - Traditional herbal medicines
  - Products for which a waiver has been granted, for example "medicines intended to treat conditions that occur only in adults".
- PIPs must be submitted in accordance with guidelines and must be agreed by the *Paediatric Committee* (PDCO). The PDCO comprises five members of the CPMP representing five EU member states, one member for each of the other 22 member states, and six representatives of patient/family and healthcare professional organizations.
- For new medicinal products, "applications for a PIP, including a deferral if relevant, and/or for a waiver should be submitted no later than the completion of the relevant human pharmacokinetic studies in adults, unless justified"(Row 21 Table 3).
- For new medicines: "Once authorisation is obtained in all EU Member States and study results are included in the product information, the medicine is eligible for six months' patent extension" (Row 21 Table 3).

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2 *Well-established medicinal use* means that the active substances in the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety as evidenced by the scientific literature (Directive 2001/83/EC, as amended)

- "Orphan-designated medicinal products are subject to the same requirements as above, and benefit from two years of market exclusivity, in addition to the 10-year exclusivity awarded under the EU Orphan Regulation".
- The requirement for a PIP also applies to applications to add a new indication (including paediatric), a new pharmaceutical form, or a new route of administration. [Comment: Will this deter such applications?]
- "Off-patent medicines developed specifically for paediatric use and with an appropriate formulation can benefit from a new marketing authorization: the paediatric-use marketing authorization (PUMA). Provided the product development follows an agreed PIP, the company will benefit from 10 years of data protection".

4.3 Documents retrieved for USA

Table 4 lists relevant documents located for the USA and provides a summary of each. The table is sorted into legislation and guidances/resources, and then by date. The original date of US legislation is not always obvious when it is published in legal registers as 'current'. Various Guidances/Resources complement the legislation and are summarized in the table.

Legislation has proceeded as follows in the USA:

- The *Food & Drug Modernisation Act* of 1997 (FDAMA) provided an additional six months of marketing exclusivity or patent protection for a drug for which FDA has requested paediatric studies and the manufacturer/sponsor has provided them.
- The *Pediatric Rule* of 1998 consolidated several existing parts of the Code of Federal Regulations (CFR). *Inter alia* it allowed FDA to require pediatric studies for a new drug or biological product if the product is likely to be used in a "substantial number of pediatric patients" or would provide a "meaningful therapeutic benefit" to pediatric patients over existing treatments, or if inadequate labeling could pose significant risks.
- The *Best Pharmaceuticals for Children Act* of 2002 reauthorized and amended the pediatric exclusivity incentive programs, and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily.
- The *Pediatric Research Equity Act* (PREA) required applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration to contain a pediatric assessment unless the applicant had obtained a waiver or deferral. It also authorized FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of these changes to submit a pediatric assessment under specified circumstances.
- In October 2002, a US Court held that FDA had exceeded its statutory authority when issuing the *Pediatric Rule*. Implementation of the rule was suspended.
- *Inter alia* the *Food and Drug Administration Amendments Act* (FDAAA) reauthorized & supplemented the detail in the *Pediatric Rule* & the *Best Pharmaceuticals for Children* Acts. The American Academy of Pediatrics has published a detailed comparison of the old and

new legislation (Row 23 Table 2). Relevant amendments are intended to further encourage[5]:

- development of safety, effectiveness & dosing information for drugs used in children
- development of specialized pediatric medical devices.

4.4 Documents retrieved for WHO

Table 5 lists relevant documents located for WHO and provides a summary of each. The table is sorted by date. Five documents are listed:

1. A World Health Assembly (WHA) resolution that in effect authorises activity in this area.
2. Definition of the problems and the topics to be addressed.
3. A tabulation of sources and prices of selected medicines for children.
4. The WHO model list of Essential Medicines for Children.
5. Various WHO publications concerning paediatric medicines.

4.5 Other documents retrieved

Table 6 lists other relevant regulatory documents located, and provides a summary of each. Several nations have addressed the question of medicines for children, implemented local guidelines and prepared plans for the future.

In relation to countries mentioned in the terms of reference:

Australia:	The TGA website references EMEA guidelines. Sponsors are encouraged to discuss requirements for medicines in specific populations such as children. There are fee waivers for low volume medicines via the *Orphan drug program*.
Brazil:	Registration guidelines were found on the DRA website (ANVISA) but did not include specific reference to paediatric medicines.
Canada:	Canada has an addendum to the ICH paediatric guideline (E11) that discusses ethical issues & additional preclinical data for paediatric medicines in various circumstances. An *Office of paediatric initiatives* was established in 2006. For details see Rows 2 & 4 of Table 6.
China:	China has no paediatric-specific requirements but informal guidelines exist. For details see Rows 4 & 5 of Table 6.
India:	No significant documents were found via the website. See Table 2 on page 16.
Russia:	There are restrictions on the conduct of clinical trials in children & on prescribing medicines & dietary supplements for disabled children. See Row 9 of Table 6.

For Japan, no relevant guidelines were found in English on the Japanese DRA (PMSB) website. The Japanese industry association (JPMA) advises as follows (see Row 7 of Table 6):

- At present, there are no laws and regulations aimed at drug development and direct promotion of information dissemination in the pediatric field.
- A *Study Group on Pediatric Drug Treatment* was established in 2006 to collect & evaluate evidence on the efficacy & safety of pediatric drug treatment, to conduct surveys on prescriptions for drugs for pediatric use & to provide information to health professionals concerning pediatric drug treatment.

5. Are there are major gaps in existing global guidelines that could help manufacturers in creating paediatric formulations?

This ToR asks what additional regulatory guidelines might encourage development of paediatric medicines

In interpreting what is meant in this context by *regulatory guidelines*, it is noted that most guidelines (or *guidances* in the USA) that are issued by regulators are advisory rather than prescriptive and it is open to applicants to offer alternative means of supporting an application. In contrast legislation is prescriptive and unalterable except by legal appeal. Consequently this term of reference has been interpreted as including advisory and informative publications. The EU *Reflections* paper is relevant in this context (Row 11 in Table 3 below).

This author is not qualified to comment on any gaps there may be in preclinical and clinical guidelines for paediatric medicines.

When developing a paediatric dosage form, it is first necessary to select the appropriate drug(s), strength(s) and dosage forms. Selections will vary with the children's age, and may alter over time as evidence accumulates.

The next question is how to proceed with pharmaceutical development. The EU has recognized the importance of this factor and has foreshadowed guidelines on the topic.

The majority of pharmaceutical manufacturers are in the private sector

In many legal jurisdictions, companies are obliged to maximize profits for shareholders, so that development of paediatric medicines is legally acceptable only if it can be shown to be consistent with maximum profits, either directly or indirectly. Without intending to take a political perspective, the difficulties in developing paediatric dosage forms are discussed below from the perspective of a manufacturer.

Commercially there are real difficulties in developing and marketing paediatric formulations.

– Sales volumes are generally low in comparison with those for adult medications. Consequently their development is not a commercial priority.

- Paediatric doses are often not defined or are not rigorously evidence-based. Even when there is a consensus, evidence may lead to changes.
- Doses are likely to vary for different paediatric age groups. Consequently, even if paediatric medications are available, there is likely to be demand from both health professionals and regulators for multiple dose options, further increasing costs and reducing profitability. Again preferences may change as evidence accumulates.
- Chemical reactions in general are favoured in the liquid state for thermodynamic and mechanistic reasons. Consequently drug-drug, drug-excipient and drug-environment (e.g. oxidative, hydrolytic, photolytic) reactions are more likely to occur and in larger proportion. That is to say: liquid dosage forms are generally less stable than are solid dosage forms and consequently are likely to have a shorter shelf life, with commercial implications.
- Younger children generally prefer liquid to solid dosage forms but many drugs have low stability in aqueous form.
- Some drugs have a bitter or otherwise unpleasant taste that can be difficult to mask in liquid form.
- The ethical, legal and logistic difficulties in conducting clinical trials in children contribute to the absence, for many drugs, of information as to pharmacokinetics, bioequivalence and suitable dose regimens. The US *Best Pharmaceuticals for Children Act* inter alia authorizes funding of relevant clinical trials by the US NIH.

From a quality perspective, paediatric dosage forms and strengths manufactured by validated procedures and to validated formulations under audited GMP conditions are preferred

Given that the required dosage forms are unlikely to be available with these desiderata in the near future, the question of extemporaneous dispensing must be addressed and must be facilitated as far as is possible consistent with product quality. Extemporaneous dispensing includes modification of marketed/registered products.

With the above considerations in mind, suitable marketed paediatric dosage forms may be encouraged by developing suitable guidelines for manufacturers

For example:

- Further develop the EC *Reflection paper*. For less well-resourced nations such redevelopment would entail preferring low cost dosage forms, and preferring dosage forms that are suitable for administration in remote areas and are stable in climatic zones III and IV.
- Review ICH, EMA and FDA guidelines for studies in paediatric populations. Either adopt these guidelines or modify them for WHO purposes.
- Prepare a list of excipients that are in general to be avoided in paediatric medicines, giving reasons in each case. Provide reasons if possible.
- Prepare a list of excipients that <u>are</u> suitable for use in paediatric medicines, together with appropriate routes of administration and again giving reasons.

- Make information available as to suitable dosage regimes for drugs that are safe and effective in the paediatric population as far as is known. *Inter alia* this will permit manufacturers to better predict the strengths that will be marketable.
- Formulate bioequivalence guidelines for generic versions of paediatric dosage forms. Bioequivalence studies can be a major and costly impediment to registration of new products. Consistent with advice in the WHO guideline concerning fixed-dose combinations, "a bioequivalence study in adults may be extrapolated to the paediatric population provided that the pharmacokinetics of all actives are well-established in both populations and it is known that there are no differences that could affect the outcome of the bioequivalence study. Extrapolation of bioequivalence data between age groups should be justified in these terms."
- Consideration should be given to extending to paediatric dosage forms the existing WHO proposal for BE waivers on the basis of the biopharmaceutical classification system.

Consideration should be given to including paediatric dosage forms in the WHO prequalification program (PQP)

It is likely that the project already encompasses paediatric dosage forms of drugs used in the treatment of HIV/AIDS, malaria and tuberculosis. To expand its coverage to all paediatric dosage forms would require additional funding.

Given that paediatric dosage forms are often not be commercially viable and may be withdrawn on commercial grounds, a model protocol could be prepared to address management of withdrawal of paediatric products

This would be of assistance to regulatory authorities, especially those that do not financial strength.

Journals should be encouraged to require information on dosage form, formulation and method manufacture in reports of studies in paediatric populations

Concerning extemporaneous dispensing:

- Guidelines should be developed for extemporaneous preparation of paediatric medicines. It may be possible to do this in collaboration with the British National Formulary for children.

DILUTION OF INJECTABLES

Injections often need to be extemporaneously diluted for paediatric use. This practice carries microbiological implications. Even if the product contains an antimicrobial preservative, dilution will render it less effective and possibly totally ineffective. If contamination is inadvertently introduced during the dilution procedure and the product is not used immediately, microbes may proliferate. The problem can be minimized by limiting storage time after the dilution procedure, and storing in a refrigerator.

- A protocol should be prepared for extemporaneous dilution of injectables with microbiological consequences in mind. The existing relevant EU guideline may either be adopted as is, or be developed for WHO purposes.
- Manufacturers should be encouraged to include information in product information concerning drug stability and physicochemical characteristics, and a guideline should be developed for this purpose. The type of information that is relevant includes primary physicochemical information on the API (active pharmaceutical ingredient) concerning for example solubility (including pH solubility profile), polymorphism, pKa, odour, taste, partition coefficient and chemical reactivity. This gives the formulator of extemporaneous medicines a basis for decision-making.
- For tablets, suppositories and possibly other solid dosage forms, product information should state whether the product can safely be halved or crushed. After halving, do the halves have adequate homogeneity? (e.g. it is known that some suppositories are not suitably homogenous). For capsules, can they be emptied and further diluted? If so, what is a suitable solid or liquid diluent to permit dose reduction (e.g. powdered lactose or starch, water or cow's milk). And, given the strength of the product, how can dilution be optimized to give a product of adequate uniformity?
- What is the stability of these diluted products (solid and liquid) in various media at suitable temperatures. For WHO purposes and in the context of less well-developed nations, suitable temperatures and humities are likely to be those nominated in WHO's stability guidelines for climatic zones III and IV.
- What is the stability of the product when crushed or diluted etc, and when they are further mixed with food and drink? Suitable foods and drinks should be of relatively reproducible composition, e.g. cow's milk, cooked rice, cooked apple, yoghurt. Foods and drinks of variable composition should be avoided, such as fruit juices (whose pH and composition can vary widely). Product information should highlight any food and drink known to be unstable when mixed with the product.

> Some products already carry this type of information. For example product information allows certain slow release theophylline capsules to be opened and the contents sprinkled on nominated foods.

- For transdermal patches and possibly other dosage forms, product information should state whether they can safely be cut, and whether subsequent dose delivery will be uniform and reproducible.
- For injectables, nebulizing solutions and possibly other dosage forms, product information should provide information on pH, osmolality and irritancy of dilutions, in addition to stability.

Table 2 Results of search of regulatory websites

Globally identified Medicines Regulatory Authority Websites	
According to WHO, this list of URLs is correct as of 011009	
Africa	
1. Algeria: http://www.ands.dz/pharmacie-med/sommaire.htm pharmacovigilance: http://www.cnpm.org.dz/	Website in French only. Email to Amor Toumi 271009
2. Angola: no website identified	-
3. Benin: no website identified	-
4. Botswana: http://www.moh.gov.bw/ - MoH - no MRA - counted as MRA because Elodie Jambert classified it as such	See file. Not special requirements found.
5. Burkina Faso: http://www.sante.gov.bf/SiteSante/ministere/sc/dgpml.html	Documents in French only. Did not find documents relating to children or registration
6. Burundi: website does not exist - only MoH	-
7. Cameroon: no website identified	-
8. Cape Verde: no website identified	-
9. Central African Rep: no website identified	-
10. Chad: website does not exist	-
11. Comoros, The: no website identified	-
12. Congo, The: no website identified	-
13. Cote d'Ivoire: no website identified	-
14. Democratic Republic of Congo: website does not exist	-
15. Equatorial Guinea: no website identified	-

16. Eritrea: website does not exist	-
17. Ethiopia: http://www.daca.gov.et/	See file. No special requirements found for children
18. Gabon: website does not exist	-
19. Gambia: no website identified	-
20. Ghana: http://www.fdbghana.gov.gh/	Nothing found on website. Email to Stephen K Opuni 271009
21. Guinea: no website identified	-
22. Guinea-Bissau: no website identified	-
23. Kenya: http://www.pharmacyboardkenya.org/	Did not find registration guidelines.
24. Lesotho: no website identified	-
25. Liberia: no website identified	-
26. Madagascar: no website identified	-
27. Malawi: no website identified	-
28. Mali: http://www.dirpharma.org/	Website in French only. Found nothing that might be registration guidelines. Parts of website were under construction.
29. Mauritania: no website identified	Website in French only. Email to Amor Toumi 271009
30. Mauritius: http://www.gov.mu/portal/site/mih MIH - no MRA - counted as MRA because Elodie Jambert classified it as such	Found nothing on website. Site not specific to health or medicines. Sent email to MoH - undeliverable.
31. Mozambique: website does not exist	-
32. Namibia: http://www.nmrc.com.na/	Registration guidelines were 2 pages
33. Niger: no website identified	-
34. Nigeria: http://www.nafdacnigeria.org/	2 pages on website. Nothing specific to children. See file.
35. Rwanda: http://www.moh.gov.rw/index.php?option=com_content&view=article&id=62&catid=56:ministry-taskforces&Itemid=1	Found nothing on website. Sent email 271009 - reply 101109 - no paediatric guidelines
36. Sao Tome & Principe: no website identified	-

37. Senegal: http://www.sante.gouv.sn/ click -les directions- and then -La Direction de la Pharmacie et des Laboratoires (DPL)-	Could not connect to website.
38. Seychelles: no website identified	-
39. Sierra Leone: website does not exist	-
40. South Africa: http://www.mccza.com/	Rang & spoke to Khamusi Mutoti. There is only one registration guideline for all medicines. See file. Nothing specific for children.
41. Swaziland: MRA is being established http://www.gov.sz/home.asp?pid=99	-
42. Togo: no website identified	-
43. Uganda: http://www.nda.or.ug/	See file. Nothing specific for children.
44. United Republic of Tanzania: http://www.tfda.or.tz/	Google recommended not visit website.
45. Zambia: no website identified	-
46. Zimbabwe: http://www.mcaz.co.zw/	See file. No special requirements found for children
The Americas	
1. Antigua and Barbuda: no website identified	-
2. Argentina: http://www.anmat.gov.ar/	In spanish only. Found no detailed registration guidelines
3. Bahamas: http://www.phabahamas.org/hospitals_overview_bnda.php	DRA is Public Hospitals Authority. No instances of *regis*
4. Barbados: no website identified	-
5. Belize: no website identified	-
6. Bolivia: http://www.sns.gov.bo/snis/enlaces_salud/dinamed/index.htm	Download caused Windows to freeze
7. Brazil: http://www.anvisa.gov.br/eng/index.htm	See file. Found no references to paediatric guidelines
8. Canada: http://www.hc-sc.gc.ca/dhp-mps/index-eng.php	See folder - Emails 261109
9. Chile: http://www.ispch.cl/	Instituto de Salud Pública de Chile. Under heading: *Instructivo para completar la solicitud de registro de producto farmacéutico nuevo (srn) informacion general*, found no instances of *niň, paed, pedi.*

10. Colombia: www.invima.gov.co/	Instituto nacional de vigilencia de medicamentos y alimentos. Website returned no instances of *child, niño, nino, paed* or *pedi*. Website is in spanish. Did not find guidelines for registration.
11. Costa Rica: http://www.ministeriodesalud.go.cr/ MoH department with information on site	"The interner reports that the item you requested could not be found"
12. Cuba: http://www.cecmed.sld.cu/	Website in Spanish. Email to Celeste 281009. Another email to celeste's direct address 061109.
13. Dominica: no website identified	-
14. Dominican Republic: http://www.drogasyfarmacias.gov.do/	Direccion general de drogas y farmacidos. Website returned no instances of *child, niño, nino, paed* or *pedi*. See file.
15. Ecuador: no website identified	-
16. El Salvador: no website identified	-
17. Grenada: no website identified	-
18. Guatemala: http://portal.mspas.gob.gt/regulacion_y_control_de_productos_farmaceuticos_y_afines.html MoH department with information on site	Ministerio de Salud Pública y Asistencia Social. Website is in spanish - did not find english option. Did not find documentation relating to medicines registration. Did not find a search (buscar) function on the website.
19. Guyana: MoH department http://www.health.gov.gy/prg_adm_food_drugs.php	MoH republic of Guyana, Food & Drug Department. Searches for *child, paed* and *pedi* retrieved nothng relevant to this project.
20. Haiti: website does not exist	-
21. Honduras: http://www.dgrs.gob.hn/	Direccion General de Regulacion Sanitaria. Formulario Solicitud de Registro o Licencia Sanitaria.pdf is 2-pages in length so unlikely to include requirements relating to paediatric medicines. Found nothing else relevant on the site.
22. Jamaica: http://www.pcoj.org/ pharmacies and pharmacists, not drugs	Pharmacy council of Jamaica. "The Pharmacy Council of Jamaica was established in August 1975 by the Ministry of Health with responsibilities for the regulation of pharmacists, pharmaceutical students, pharmacy owners and authorized sellers of poisons in accordance with The Pharmacy Act (1966)". Found nothing on website concerning child or registration of medicines.

23. Mexico: http://www.cofepris.gob.mx/	Sitre in spanish only. Could not find registration guidelines. "Contacto" function did not work.
24. Nicaragua: no website identified	-
25. Panama: http://www.minsa.gob.pa/ MoH department with information on site	Dirección Nacional de Farmacia y Drogas. Found *Programa de Niñez Y Adolescencia* but there was no hyperlink.
26. Paraguay: http://www.mspbs.gov.py/programas/index.php?id=6	Direccion Nacional de Vigilancia Sanitaria. Found *Renovación de registro sanitario de productos armacéuticos* ReProF - 21 pages. Search found no instances of *niñ*
27. Peru: http://www.digemid.minsa.gob.pe/	*Direccion generale de medicamentos, insumos y drogas.* The search function did not operate. Found no guidelines relating to registration or requirements therefore. Site is in Spanish.
28. Saint Kitts and Nevis: no website identified	-
29. Saint Lucia: no website identified	-
30. Saint Vincent and the Grenadines: no website identified	-
31. Suriname: no website identified	-
32. Trinidad and Tobago: http://www.health.gov.tt/sitepages/default.aspx?id=93	Ministry of health, *Chemistry, Food and Drug Division*. A user-friendly site! Found no instances of *child, paed* or *pedi*.
33. United States of America: http://www.fda.gov/	see file
34. Uruguay: http://www.msp.gub.uy/subcategorias_8_1.html	*Ministerio de Salud Pública*. Found nothing relating to children or to registration guidelines.
35. Venezuela (Bolivarian Republic of): http://www.inhrr.gov.ve/	*Ministerio del podar popular para la saludad. Instituto nacional de higiene.* Found nothing relating to children or to registration guidelines.
The Eastern Mediterranean	
1. Afghanistan: website does not exist - only MoH	-
2. Bahrain: no website identified	-
3. Djibouti: no website identified	-

4. Egypt: http://www.eda.mohp.gov.eg/	Found no registration guidelines at all on website. Sent email 281009
5. Iran (Islamic Republic of): no website identified	-
6. Iraq: no website identified	-
7. Jordan: http://www.jfda.jo/en/default/	Link to "Check List Regarding Documents Submitted For Drug Registration Purposes" at http://www.jfda.jo/EN/Forms/details.aspx?id=48. Link did not work. Sent email to info@jfda.jo 281009
8. Kuwait: no website identified	-
9. Lebanon: http://cms1.omsar.gov.lb/en/Drugs/DrugsListWithLinks.htm.	http://cms1.omsar.gov.lb/en/ - Ministry of Public Health. Under Drugs, no finds after search for regis. General search for regis…..nothing retrieved
10. Libyan Arab Jamahiriya: no website identified	-
11. Morocco: http://srvweb.sante.gov.ma/Medicaments/Pages/default.aspx	Royaume de Maroc. *Ministere de la sante*
12. Oman: http://www.moh.gov.om/nv_menu.php?fNm=pharma/regulation.htm	Found Regulation for Pharmaceutics. Google translation found no instances of *paed* or *pedi.* Two instances of *child* referred to content of alcohol in medicines.
13. Pakistan: http://www.dcomoh.gov.pk/	See file No paediatric-specific guidelines found
14. Qatar: http://www.nha.org.qa/moh/ under construction	-
15. Saudi Arabia: http://www.sfda.gov.sa/En/Home/default.htm	No paediatric guidelines listed at http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm See files x 2
16. Somalia: no website identified	No instances of *regis*
17. Sudan: http://www.nmpb.gov.sd/	*National medicines & poisons board*. See file. In General Requirements for the Registration of Pharmaceutical Products, no instances of *child, paed, pedi*
18. Syrian Arab Republic: no website identified	-
19. Tunisia: http://www.dpm.tn/	English section of website under construction. Email to A Toumi 271009
20. United Arab Emirates: http://www.moh.gov.ae/en/Page_431.aspx	"Check List for Receiving a Dossier for Registration of conventional Medicinal Product" <-- link did not function. See file "UAE Appn Regn Med Conv Prod 281009.pdf". No hits for *child, paed, pedi*.
21. Yemen: no website identified	-

Europe	
1. Albania: http://www.qkkb.gov.al/	QKKB *Qendra Kombetare e Kontrollit te Barnave - National center for the control of drugs*. Has an English option. No relevant documents found. Email to regjistrim@qkkb.gov.al 031109.
2. Andorra: http://www.salutibenestar.ad/ MoH department with information on site	Website under maintenance & not functioning
3. Armenia: http://www.pharm.am/index.php?langid=2 http://www.pharm.am/index.php?langid=2	New website found 190110. *Scientific centre of drug & medical technology expertise* (SCDMTE). "Requirements to the State Registration of Drugs in the Republic of Armenia (Coming soon) (Download) File available in Armenian"
4. Austria: http://www.ages.at/ages/ueber-uns/english-what-is-ages/	Found page: http://www.basg.at/arzneimittel/kinderarzneimittel/ but did not find english translation. See file
5. Azerbaijan: http://www.pharm.az/ under construction	No info on this site. Check back soon! Same message at 190110.
6. Belarus: http://www.rceth.by/	Website is in Russian. Found 'Sample application for implementation of the state sanitary regulation and registration (for domestic producers)' - it downloaded in ?Russian.
7. Belgium: http://www.fagg-afmps.be/ : Federal Agency for Medicines and Health Products	An application for marketing authorisation for a medicine for human use must be submitted in CTD format. Belgium national document eSubmission guideline v.2.8 (PDF, 225.68 Kb) is an adaptation of EMEA's http://esubmission.emea.europa.eu/new.htm.
8. Bosnia and Herzegovina: http://www.alims.gov.ba/	The main language of the website is in ?Russian. The English section of the website is under construction.
9. Bulgaria: http://www.bda.bg/	English language parts of site are under construction.
10. Croatia: http://www.almp.hr/?ln=en&w=o_agenciji	Marketing authorisation procedure page is under construction
11. Cyprus: http://www.moh.gov.cy/moh/phs/phs.nsf/dmlindex_en/dmlindex_en?opendocument	Found nothing on the website except a ref to EU registration requirements. Cyprus is now part of EU so may not have separate requirements.
12. Czech Republic http://www.sukl.cz/	Uses eCTD - see file. Found also Application for renewal of marketing autorisation but no instances of *child, paed* or *pedi*

13. Denmark: http://www.dkma.dk/	*Laegemiddel styrelson - Danish Medicines Agency*. Email to Sue & Lembit 301009 re need to pay for guidelines. Most likely to be those of EU.
14. EMEA: http://www.emea.europa.eu/ (also: DG Enterprise)	see file
15. Estonia: http://www.sam.ee/ State Agency of Medicines (SAM)	http://www.ravimiamet.ee/735. No significant findings for child, paed or ped. See file.
16. Finland: http://www.nam.fi/	*National agency for medicines* - uses EMEA procedures - see file
17. France: http://www.afssaps.fr/	AFSSAPS : *Agence française de sécurité sanitaire des produits de santé*. See folder. There are a number of paediatric initiatives. Reference is made to EU regulation 1901/2006 (see elsewhere).
18. Georgia: http://gdna.georgia.gov/02/gdna/home/0,2803,132319894,00.html	GDNA *Georgia drugs and narcotics agency*. No significant findings for *child, paed* or *pedi*.
19. Germany: http://www.bfarm.de/gb_ver/ and: http://www.zlg.nrw.de/ and http://www.pei.de/EN/home/node-en.html?__nnn=true	BfArM *Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte).* See folder. Did not find any specific guidelines other than those of EMEA, except for labelling, SPC etc
20. Greece: http://www.eof.gr/web/guest/home	National organisation for medicines. Found no guidelines for regsitration. No instances of child
21. Hungary: http://www.ogyi.hu/main_page/	*Országos Gyógyszerészeti Intézet. National institute of pharmacy*. See file. National procedure refers to EU guidelines - see file
22. Iceland: http://www.imca.is/	*Lyfjastofnun - Icelandic medicines control agency*. See file. Apparently the same application forms apply to all types of application - so all are those of EMEA
23. Ireland: http://www.imb.ie/	*Irish medicines board*. See file. Guidelines for national procedure appear to be same as for EMEA.
24. Israel: http://www.health.gov.il/ MoH department with information on site	http://www.health.gov.il/english/. Ministry of health. Most of website in Hebrew - some english sections. See file. No relevant instances found for child, paed or pedi.

25. Italy: http://www.aifa.gov.it/ and http://www.agenziafarmaco.it/section8983.html	*AIFA agenxia italiano del farmaco*. No instances of *paed or pedi*. For instances of *child* - there is an Italian version of British Medicines for children entitled *Guide to use of medications for children.*
26. Kazakhstan: http://www.dari.kz/?lang=rus	Website is in Russian. Did not find an English option. Search for *child, paed or pedi* retrieved no hits
27. Kyrgyzstan: http://pharm.med.kg/	Website only in Russian. Found nothing in English.
28. Latvia: http://www.vza.gov.lv/index.php?setlang=en&large	*State Agency of Medicines of Latvia*. Did not find registration guidelines for medicines.
29. Lithuania: http://www.vvkt.lt/index.php?3327723903	*Valstybine vaistu kontroles tarnyba* (VVKT). The section *For Pharmacy Companies* is under construction. The section *medicines registration* linked to an EMEA template: http://www.emea.europa.eu/htms/human/qrd/qrdplt/HqrdtemplateIt.doc.
30. Luxembourg: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html MoH department with information on site	Website is in French. Appears to refer to EMEA documentation.
31. Malta: http://www.medicinesauthority.gov.mt/	*Medicines authority. Awtorita dwa el-medicini*. Found nothing relating to children. Limited information on this site. Did not find a search option.
32. Monaco: no website identified	-
33. Montenegro: http://sntcg.com/ulms/	*Agencija za lijekove i medicinska sredstva*. Found nothing specific to children. Limited information on this site. No English option.
34. Netherlands: http://www.cbg-meb.nl/	*College ter Beoordeling van Geneesmiddelen* CBG*, Medicines Evaluation Board* MEB. See file. Reference is made to the EU Paediatric Committee. A local Consultative Paediatricians Group has been established. Its functions include further research into the use of existing medicinal products in children and development of new pharmaceutical forms of existing medicinal products for children.
35. Norway: http://www.legemiddelverket.no/templates/InterPage____16645.aspx?filterBy=CopyToGeneral	*Norwegian Medicines Agency or Statens Legemiddelverck*. See file. EU regulation 1901/2006 is implemented. There is a campaign "to improve reporting of adverse reactions in children".

36. Poland: http://www.bip.urpl.gov.pl/	<-- this web address 'invalid'. Ministerstwo Zdrowia. Found no instances of child. Info re regn was minimal. http://www.mz.gov.pl/wwwmz/index?mr=b42841&ms=284&ml=pl&mi=512&mx=0&ma=261 concerns authorisation of med prodcs.
37. Portugal: http://www.infarmed.pt/	References EMEA guidelines. See file.
38. Republic of Moldova: http://www.amed.md/index_eng.html	*Medicines agency: Agenţia Medicamentului*. See file. No reference to *child* etc under 'Authorisation - Evaluation department' or 'Medicines authorisation clinical evaluation and pharmacovigilence department'
39. Romania:http://www.anm.ro/en/home.html	*National Medicines Agency* or *Agentia nationala a medicamentului.* No instances of *child, paed* or *pedi*.
40. Russian Federation: http://www.roszdravnadzor.ru/	DRA is Roszdravnadzor. Website is in Russian. Awaiting info from Olexander.
41. San Marino: no website identified	-
42. Serbia: http://www.alims.gov.rs/	http://www.alims.gov.rs/index_eng.php Agencija za lekove i medicinska sredstva Srbije (ALIMS) or Medicines and Medical Devices Agency of Serbia. Found no reference to guidelines relating to children. See file. EU directives are referenced.
43. Slovakia: http://www.sukl.sk/en	*State institute for drug control* SIDC. Found no instances of *child, paed* or *pedi.*
44. Slovenia: http://www.jazmp.si/index.php?id=56	JAZMP or *Agency for Medicinal Products and Medical Devices of the republic of Slovenia*. Pharmacovigilance part of site is under construction. Minimal information on site. Found nothing specifically related to paediatric mediciness except a cross reference to EU regulation 1901/2006. See file.
45. Spain: http://www.agemed.es/en/actividad/sgInspeccion/home.htm	Minimal information found on site. No relevant instances of *child, paed* or *pedi*.
46. Sweden: http://www.lakemedelsverket.se/english/	See file. The EU paediatric committee is described. Found no other instances of *child, paed* or *pedi*.

47. Switzerland: http://www.swissmedic.ch/index.html?lang=en	Reference is made to EMEA guidelines. See folder. “Several documents on this [paediatric part of the] website are available in German or French only. The text below is therefore provided in its original language. Thank you for your understanding”.
48. Tajikistan: under construction http://health.tj/en/index.php?option=com_content&task=view&id=6&Itemid=7	-
49. The former Yugoslav Republic of Macedonia: no website identified	-
50. Turkey: http://www.iegm.gov.tr/	*Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy*. See file. List of guidelines and guidances made no mention of *child, paed* or *pedi*
51. Turkmenistan: no website identified	-
52. Ukraine: http://www.pharma-center.kiev.ua/view/en/index	*State Pharmacological Centre*. A Russian language guideline is available - see *Russian language gs Ukraine.doc*. An English summary is available in *Paediatrics_WHO_Ukraine_amended 091009.doc*. See folder.
53. United Kingdom: http://www.mhra.gov.uk/index.htm	The MHRA website provides a useful summary of regulation of paediatric medicines, based largely on EMEA guidelines. See folder.
54. Uzbekistan: no website identified	-
South-East Asia	
1. Bangladesh: http://www.ddabd.org/	See file. Application form for non-pharmacopoeal drugs does not mention children. Application guidelines are in ?Bengali
2. Bhutan: http://www.health.gov.bt/dra.php	*Drug regulatory authority, Kingdom of Bhutan*. Found several references to guidelines concerning child health but none directly relevant to this project.
3. DPR Korea: no website identified	-
4. Democratic Republic of Timor Leste: website does not exist	-

5. India: http://cdsco.nic.in/	*Central Drugs Standard Control Organization*. Found Requirements for permission of new drugs approval but did not find relevant reference to *child, paed* or *pedi*. See folder
6. Indonesia: http://www.pom.go.id/e_default.asp	*Badan POM - Badan pengawas obat dan makana*. *National agency of food & drug control*. See file. Did not find forms C2-D5 mentioned in that file. Email 221109 "I am undertaking a project for WHO EDM to review international regulatory guidelines for paediatric medicines. Can you help me pls with information as to whether Indonesia has paediatric-specific guidelines? Your response would be much appreciated. With thanks"
7. Maldives: http://www.mfda.gov.mv/web/	*Maldives food & drug authority*. Neither the 'Pharmaceuticals' nor 'Regulation & standards' sections of website contain any text as yet.
8. Myanmar: no website identified	-
9. Nepal: http://www.dda.gov.np/reg_modern_medicine.php	Found no guidelines relating to paediatric medicines. See file.
10. Sri Lanka: http://203.94.76.60/DRA/home.htm	*Drug regulatory authority of Sri Lanka*. Website is in English. Found nothing relevant. Sent email 221109 "Dear Sri Lankan medicines regulatory authority - I am undertaking a project for Who's EDM to review international regulatory guidelines for paediatric medicines. Can you help me pls with information as to whether Sri Lanka has paediatric-specific guidelines? Thank you and best wishes"
11. Thailand: http://www.fda.moph.go.th/eng/index.stm	*Food & drug administration*. See file - found no relevant advice.
Western Pacific Region	
ASEAN	
1. Australia: http://www.tga.gov.au/	Reference to EMEA guidelines. Limited additional guidance. See file. Australia has a *Paediatric medicines advisory group* constituted via the Pharmaceutical benefits division of the Department of Health & Ageing.
2. Brunei Darussalam: http://www.moh.gov.bn/pharmacyservices/drugregistration.htm	Found no reference on website to requirements for registration
3. Cambodia: no website - only MoH	-
4. China: http://www.sfda.gov.cn/	No relevant information found on website. See folder.

a. Hong Kong (China) SAR: http://www.psdh.gov.hk/eps/index.jsp	*Pharmaceutical service, Department of Heal*th. File *HongKong gs regn 051109.pdf* contains no relevant instances of *child, paed* or *pedi.* Website search found no instances of *child, paed* or *pedi.*
5. Cook Islands: no website identified	-
6. Fiji: http://www.health.gov.fj/FPS/insRA.html	*Fiji pharmaceutical & biomedical services centre - Fijipharmac.* Found nothing specific to this project. See file.
7. Japan: http://www.pmda.go.jp/english/index.html	Found nothing relevant on the website. See folder for information from Japanese manufacturers' association.
8. Kiribati: no website identified	-
9. Lao's People's Democratic Republic: no website identified	-
10. Malaysia: http://www.bpfk.gov.my/ http://www.pharmacy.gov.my/index.cfm	*National pharmaceutical control bureau*. See file. Found no relevant instances of *child, paed* or *pedi*.
11. Marshall Islands: no website identified	-
12. Micronesia, Federated States of: no website identified	-
13. Mongolia: http://www.moh.mn/ MoH, http://www.ssia.gov.mn/ state specialized inspection agency, http://www.doh.gov.mn/ Department of Health	Website is in Russian. Did not find English option. Google did not translate the text. Site search found no instances of *child, paed* or *pedi* (not surprising given lack of English text).
14. Nauru: no website identified	-
15. New Zealand: http://www.medsafe.govt.nz/	See file. Found nothing of significance.
16. Niue: no website identified	-
17. Palau: no website identified	-
18. Papua New Guinea: website does not exist	-
19. Philippines: http://www.bfad.gov.ph	Link to registration requirements did not function. Sent email 281009.
20. Republic of Korea: http://ezdrug.kfda.go.kr/	Website in ?Korean. Search function returned no instances of *child, paedi* or *pedi*

21. Samoa: no website identified	-
22. Singapore: http://www.hsa.gov.sg/publish/hsaportal/en/home.html	See files. Found no instances of *child, paed* or *pedi*
23. Solomon Islands: no website identified	-
24. Tonga: no website identified	-
25. Tuvalu: no website identified	-
26. Vanuatu: no website identified	-
27. Vietnam: http://www.dav.gov.vn/	*Drug administration of Vietnam*. Website is in ?vietnamese. Google translation did not disclose relevant documents.

make medicines child size

Table 3 Documents retrieved for Europe with summaries

Sorted into legislation, concept papers & guidelines/resources Then sorted by date

	DOCUMENT		NOTES
LEGISLATION			
1	Title: Country/region: Publisher: Date: URL or other ref: File name:	Regulation (EC) No 1901/2006 "on medicinal products for paediatric use". EU European Commission 12 Dec 2006 See footnotes 3·4 EU 1901-2006 regulation.pdf	"This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorized for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations". The content of the regulation is summarised in the leaflet "Better medicines for children" [see elsewhere in this report].
2	Title: Country/region: Publisher: Date: URL or other ref: File name:	Regulation (EC) No 1902/2006 amending Regulation 1901/2006 on medicinal products for paediatric use. EU European Commission 20 Dec 2006 See footnote 5 EU 1902-2006 regulation.pdf	Makes minor amendments to the wording of Regulation (EC) No 1901/2006.

3 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:EN:PDF

4 http://www.ema.europa.eu/htms/human/paediatrics/regulation.htm

5 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf

	DOCUMENT		NOTES
3	Title: Country/region: Publisher: Date: URL or other ref: File name:	Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals EU European Commission Effect date July 2008 See footnote 6 PIP format & content EMA 08.pdf	The content is self evident
CONCEPT PAPERS			
4	Title: Country/region: Publisher: Date: URL or other ref: File name:	Concept paper on the development of a quality guideline on pharmaceutical development of medicines for paediatric use Europe EMEA July 2008 See footnote 7 EMEA quality devt paeds concept paper 08.pdf	"This concept paper is intended as the first step to a scientific and harmonised approach to the development of a guideline that provides adequate tools for responsible development of a medicinal product for use in these different subsets of the paediatric population". The Annex defines principles to be applied in the assessment of Paediatric Investigation Plans, Marketing Applications, Scientific Advices (sic) and variations". Principles: - Excipients in the formulation & the means of administering the dose should be chosen with particular care. It is reasonable to expect that companies will develop formulations that avoid unnecessary exposure of sensitive patients in the long term. - Industrially-manufactured & controlled medicines are preferred to those prepared extemporaneously. - The first issue to be established is the 'criticality' of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window, etc.) and how the dose is to be calculated.

6 http://www.ema.europa.eu/pdfs/human/paediatrics/Guideline_2008_C243_01.pdf
7 http://www.ema.europa.eu/pdfs/human/qwp/13893108en.pdf

	DOCUMENT		NOTES
			- The principle of benefit / risk balance should be applied to assess the suitability of formulations, administration devices and packaging and user instruction in paediatric medicines. For example, an excipient which raises a minor safety concern may still be allowed in exceptional cases taking into account the seriousness of the clinical indication, or the advantages offered by a particular pharmaceutical form, route of administration, or duration of treatment, etc.
5	Title: Country/region: Publisher: Date: URL or other ref: File name:	Need for the development of a paediatric addendum to the note for guidance on the clinical investigation on medicinal products in the treatment of hypertension EU EMEA Dec 2008 See footnote 8 Hypertension paed EU concept paper 1208.pdf	Concept paper
6	Title: Country/region: Publisher: Date: URL or other ref: File name:	Need for the development of a paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension EU EMEA Jan 2009 See footnote 9 Hypertension pulm paed EU concept paper	Concept paper

8 http://www.ema.europa.eu/pdfs/human/ewp/54545608en.pdf

	DOCUMENT		NOTES
		0109.pdf	
7	Title: Country/region: Publisher: Date: URL or other ref: File name:	Need for the development of a paediatric addendum to the CHMP note for guidance on the clinical investigation of medicinal products in the treatment of lipid disorders. EU EMEA Jan 2009 See footnote 10 Lipid disorders paed EU concept paper 0109.pdf	Concept paper
GUIDELINES/RESOURCES			
8	Title: Country: Publisher: Date: URL or other ref: File name:	Evaluation of anticancer medicinal products in man: Addendum on paediatric oncology EU EMEA Effect date Jan 2004 See footnote 11 EMEA paed oncology Add 04.pdf	"The [EMEA] Note for Guidance on Evaluation of Anticancer Medicinal Products in Man addresses general regulatory aspects in anticancer drug development and [it] is generally applicable for drugs intended for childhood malignancies. The aim of this Addendum is to complement the current guideline with more specific requirements related to paediatric oncology and to provide more specific information on the design and conduct of phase I trials in paediatric cancer patients". Topics addressed include (1) preclinical studies in models predictive of paediatric tumours and (2) design of phase I trials in children with cancer. The latter includes eligibility criteria, starting dose and subsequent dose levels, and comparison of pharmacokinetics/systemic exposure between adults and children.
9	Title:	Note of Explanation to accompany publication of Reflection Paper on	"Th[e] reflection paper *[see elsewhere]* was produced with two main aims:- (a) to provide general information or 'points to consider' for those in the pharmaceutical industry who may have little

9 http://www.ema.europa.eu/pdfs/human/ewp/64426108en.pdf
10 http://www.ema.europa.eu/pdfs/human/ewp/789509en.pdf
11 http://www.ema.europa.eu/pdfs/human/ewp/056902en.pdf

	DOCUMENT		NOTES
		Formulations of Choice for the Paediatric Population.	experience of the issues when formulating medicines for children, and (b) to serve as the precursor to a guideline on the subject by stimulating those with most experience to contribute their additional and more specific information, experience and opinion to the framework presented". "Whilst the objective of this document is to encourage the pharmaceutical industry to develop authorised ready-made paediatric dosage forms which do not need such manipulations, the CHMP recognises that until such time as medicines which are clearly useful in paediatric patients are legitimately authorised and presented in a suitable form for this population, there will remain a gap where pharmacists and caregivers may need to manipulate adult medicines in exceptional cases, for the benefit of paediatric patients. Therefore, a further aim has been to highlight the risks attached to these manipulations and readers are requested to comment on the way in which the pharmaceutical industry and practitioners might make such manipulations safer and more effective".
	Country:	EU	
	Publisher:	EMEA	
	Date:	June 2005 (before adoption of the final Reflection Paper)	
	URL or other ref:	See footnote 12	
	File name:	EMEA reflections paed meds notes 05.pdf	
10	Title:	EMEA/PEG procedure for identifying paediatric needs	Defines a procedure for identifying research and development needs relating to paediatric medicines by consultation with experts, learned societies and national authorities.
	Country:	EU	
	Publisher:	EMEA	
	Date:	June 2005	
	URL or other ref:	See footnote 13	
	File name:	EMEA paed needs assment note 05.pdf	
11	Title:	Reflection paper: Formulations of choice for the paediatric population.	A summary of the physiological and pharmaceutical issues to be taken into account in developing and assessing medicines for paediatric use.
	Country:	EU	
	Publisher:	EMEA	
	Date:	Adopted Sept 2006	
	URL or other ref	See footnote 14	

12 http://www.ema.europa.eu/pdfs/human/paediatrics/19621805en.pdf
13 http://www.ema.europa.eu/pdfs/human/paediatrics/17519205en.pdf

	DOCUMENT		NOTES
	File name:	EMEA reflections paed meds 06.pdf	
12	Title:	Inventory of Community and Member State rewards and incentives to support research into, and the development & availability of, medicinal products for paediatric use	
	Country/region:	Europe	
	Publisher:	EMEA	
	Date:	Dec 2006	
	URL or other ref:	See footnote 15	
	File name:	Rewards & incentives implemented EU 1206.pdf	
13	Title:	Joint European Commission / EMEA Document: Priorities for Implementation of the Regulation on Medicinal Products for Paediatric Use	
	Country/region:	Europe	
	Publisher:	EC/EMEA	
	Date:	Dec 2006	
	URL or other ref:	See footnote 16	
	File name:	Rewards & incentives implemented EU 1206.pdf	

14 http://www.ema.europa.eu/pdfs/human/paediatrics/19481005en.pdf
15 http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/inventory_on_paediatrics_07-2008.pdf
16 http://www.ema.europa.eu/pdfs/human/paediatrics/EC_EMEA_Paediatric%20Regulation.pdf

	DOCUMENT		NOTES
14	Title: Country/region: Publisher: Date: URL or other ref: File name:	Role of pharmacokinetics in the development of medicinal products in the paediatric population - Corrigendum Europe EMEA Effect date Jan 2007 See footnote 17 EMEA pkinetics paeds corrigendum 0606.pdf	"It is the objective of this document to provide recommendations in the following areas: 1 Use of pharmacokinetics and pharmacokinetic-pharmacodynamic relationships (PK/PD) in efficacy and safety assessments 2 Study design: stratification for age, specific age-related considerations, control groups 3 Data analysis, presentation and evaluation of the results, and 4 Description of the results in the Summary of Product Characteristics". Uses ICH age classification parameters. Permits use of population pharmacokinetics.
15	Title: Country/region: Publisher: Date: URL or other ref: File name:	Guideline on conduct of pharmacovigilance for medicines used by the paediatric population. EU EMEA Effect date Jan 2007 See footnote 18 EMEA ADRs paed meds 07.pdf	An extension of the ICH guideline for pharmacovigilance to the paediatric population. Includes consideration of: - The role and responsibilities of different stakeholders - Special characteristics of paediatric pharmacovigilance - Clinical safety and pharmacovigilance before authorisation of a paediatric indication - Pharmacovigilance for products on the market including 'offlabel' use, data collection, Periodic Safety Update Reports, Post authorisation safety studies, Signal Detection.
16	Title: Country/region: Publisher:	The European paediatric initiative: History of the Paediatric Regulation EU EMEA	A 3-page history to July 2007.

17 http://www.ema.europa.eu/pdfs/human/ewp/14701304en.pdf
18 http://www.ema.europa.eu/pdfs/human/phvwp/23591005enfinal.pdf

	DOCUMENT		NOTES
	Date:	July 2007	
	URL or other ref:	See footnote 19	
	File name:	History paed rule EU 0707.pdf	
17	Title:	Guidance on the content and the format of data to be collected by the Member States on all existing uses of medicinal products in the paediatric population	
	Country/region:	Europe	
	Publisher:	EMEA	
	Date:	Oct 2007	
	URL or other ref:	See footnote 20	
	File name:	Content & format data paed needs EU 1007.pdf	
18	Title:		
	Country/region:	EU	
	Publisher:	European Commission	
	Date:	Effect date July 2008	
	URL or other ref:	See footnote	
	File name:		
19	Title:	Revised priority list for studies into off-patent paediatric medicinal products	"The objective of the revision of the priority list is to provide the basis for the work programme for the Third Call for Framework Programme 7 of the European Commission. It ensures that funds are directed into research of medicinal products with the highest need in the paediatric population".

19 http://www.ema.europa.eu/pdfs/human/paediatrics/1796704en.pdf
20 http://www.ema.europa.eu/pdfs/human/paediatrics/5756962007en.pdf

	DOCUMENT		NOTES
	Country/region:	EU	
	Publisher:	EMEA	
	Date:	Effect date Aug 2008	
	URL or other ref:	See footnote 21	
	File name:	EMEA paed priorities 0808.pdf	
20	Title:	Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications	"The main aim of non-clinical studies to support the development of medicinal products to be used in paediatric patients is to obtain information on the potentially different safety profiles from those seen in adults. Juvenile animal studies can be used to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. Serious adverse reactions that may be irreversible are of particular concern. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted if there is a need to further address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors. The guideline also makes recommendations on the timing and utility of juvenile animal studies in relation to phases of clinical development." "Approval of medicinal products intended for paediatric patients requires a special risk/benefit assessment, where the possible effects of the product on the ongoing developmental processes in the age group(s) to be treated are also taken into consideration. This risk/benefit assessment should be based on safety and pharmacokinetic data from non-clinical and clinical studies. In some instances, additional studies in juvenile animals will be required to allow such an assessment. There are several examples of medicinal products that have different safety profiles in adult compared with paediatric patients. Such differences might be qualitative and/or quantitative, immediate and/or delayed. They might be caused by pharmacokinetic/dynamic differences, developmental differences in growth and function of target organs or expression of receptor systems, immune system maturation, body weight etc".
	Country/region:	Europe	
	Publisher:	EMEA	
	Date:	Effect date Aug 2008	
	URL or other ref:	See footnote 22	
	File name:	EMEA NonClin testing paed meds0108.pdf	

21 http://www.ema.europa.eu/pdfs/human/paediatrics/22698308en.pdf
22 http://www.ema.europa.eu/pdfs/human/swp/16921505en08.pdf

	DOCUMENT		NOTES
21	Title: Country/region: Publisher: Date: URL or other ref: File name:	Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006 Europe EC/EMEA Last update Sept 2008 See footnote 23 FAQs EU Paed Regulation 0908.pdf	Includes advice as to timing of the submission of PIPs & generation of data, how to apply for a waiver, deferral or exemption, incentives & rewards for generating data, & availability of scientific advice from EMEA.
22	Title: Country/region: Publisher: Date: URL or other ref: File name:	Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) & on the information to be made public by the EMEA Europe EMEA Feb 2009 See footnote 24 EU info paed CTs 09.pdf	Provides guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the EMEA.
23	Title: Country/region:	Better medicines for children Europe	The leaflet is an overview of the effect of the EU Paediatric Regulation of Jan 2007. These are some extracts: **A new Paediatric Regulation[1] entered into force in the EU on 26 January 2007**

23 http://www.ema.europa.eu/pdfs/human/paediatrics/52008506en.pdf
24 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_c28_01/2009_c28_01_en.pdf

	DOCUMENT		NOTES
	Publisher: Date: URL or other ref: File name:	EMEA 2009 See footnote 25 EMEA Better Meds Children leaflet 09.pdf	The objective of the Paediatric Regulation is to improve the health of children in Europe by: - facilitating the development and availability of medicines for children aged 0 to 17 years, - ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately, and - improving the availability of information on the use ofmedicines for children without: - subjecting children to unnecessary trials, or - delaying the authorisation of medicinal products for use in adults. **New rewards, incentives and obligations for pharmaceutical companies** **For unauthorised medicinal products** As of July 2008, marketing-authorisation applications for new products not authorised in the EU prior to 26 January 2007 have to include the results of studies conducted in the paediatric population, in compliance with an agreed PIP, unless the EMEA has granted a deferral or waiver for their provision. Waivers may be granted for medicines intended to treat conditions that occur only in adults (a list of such conditions has been agreed by the PDCO), and for medicines that may be unsafe or ineffective, or do not offer significant therapeutic benefit and/or fulfil a therapeutic need in children. Once authorisation is obtained in all EU Member States and study results are included in the product information, the medicine is eligible for six months' patent extension. Orphan-designated medicinal products are subject to the same requirements as above, and benefit from two years of market exclusivity, in addition to the 10-year exclusivity awarded under the EU Orphan Regulation. Some medicines, such as generics, are exempt from these requirements. **For authorised, patented medicinal products** As of 26 January 2009, the requirements described above also apply to applications to vary a marketing authorisation to add a new indication (including paediatric), a new pharmaceutical form, or a new route of administration. In these cases, the PIP and/or waiver must cover all existing and new indications, formulations and routes of administration. **Paediatric-use marketing authorisation (PUMA)** Off-patent medicines developed specifically for paediatric use and with an appropriate formulation can benefit from a new marketing authorisation — the paediatric-use marketing authorisation. Provided the product development follows an agreed PIP, the company will benefit from 10 years of

25 http://www.ema.europa.eu/pdfs/human/paediatrics/leaflet.pdf

	DOCUMENT	NOTES
		data protection. **Paediatric investigation plans (PIPs)** A drug-development plan — known as a paediatric investigation plan — must be agreed in advance by the EMEA's Paediatric Committee. The PIP shall cover the timing and measures proposed to obtain a paediatric indication, with an age-appropriate formulation, in all paediatric subsets affected by the condition. Once agreed by the PDCO, the PIP is binding on companies developing a medicinal product for the EU. In some cases, the product will have to be fully developed in children before applying for a marketing authorisation. In other cases, the development can be deferred until there are sufficient data to demonstrate the efficacy and safety of the product in adults. If new information becomes available during the medicine's development, it may be necessary to apply to the PDCO for a modification of the agreed PIP. **The Paediatric Committee** A Paediatric Committee (PDCO) was established at the EMEA in 2007. The main responsibility of the PDCO is to decide on the content of paediatric investigation plans. The PDCO will establish an inventory of paediatric needs in 2009, based on a survey of all existing uses to be carried out by the EU Member States. EU funding is available for paediatric research, especially for products that are off-patent and identified as a priority. **Improved communication and transparency of paediatric information** The Paediatric Regulation establishes measures to improve information on paediatric medicines. Product information (summary of product characteristics and package leaflet) will include information from efficacy and safety studies conducted in children, including when study results are negative. Information on EMEA decisions on PIPs and waivers is made public (after deletion of commercially confidential data). Results of paediatric clinical trials performed both inside and outside the EU will be published in the EU clinical trials database (EudraCT).
24	Title: List of paediatric needs (as established by the Paediatric Working Party) for anaesthesiology, anti-infectious therapy, cardiology, chemotherapy I (cytotoxic	

26 http://www.ema.europa.eu/htms/human/paediatrics/inventory.htm

	DOCUMENT		NOTES
		therapies), chemotherapy II (supportive therapy), diabetes (types I and II), epilepsy, gastroenterology, immunology, migraine, nephrology, obstructive lung disease, pain, psychiatry, rheumatology	
	Country/region:	Europe	
	Publisher:	EMEA	
	Date:	Downloaded 190110	
	URL or other ref:	See footnote 26	
	File name:	Paed needs website EU 190110.docx	
25	Title:	Investigation of medicinal products in the term & preterm neonate	"This guideline addresses the considerations and requirements for the design and conduct of clinical trials in premature and term neonates using medicinal products of relevance for the use by this population. It includes background information on the maturation of organs and of body functions".
	Country/region:	Europe	
	Publisher:	EMEA	
	Date:	Effect date Jan 2010	
	URL or other ref:	See footnote 27	
	File name:	EMEA Investgn term & preterm neonates 2010.pdf	
26	Title:	Website: Medicines for children - Paediatric medicines group	A list of guidelines applying to paediatric medicines.
	Country/region:	Europe	
	Publisher:	EMEA	

27 http://www.ema.europa.eu/pdfs/human/paediatrics/53681008enfin.pdf

	DOCUMENT		NOTES
	Date:	Downloaded 100110	
	URL or other ref:	See footnote 28	
	File name:	EMEA paed website 100109.doc	

28 http://www.emea.europa.eu/htms/humanpeg/peg.htm

Table 4 Documents retrieved for the USA with summaries

Sorted into legislation & guidances/resources
Then sorted by date

	DOCUMENT		NOTES
LEGISLATION			
1	Title: Country: Author: Date: URL or other ref: File name:	Food & Drug Modernisation Act USA FDA November 1997 See footnote 29 FDAMA 97.pdf	From reference [2]: "In November 1997, Congress enacted FDAMA, which [inter alia] contains the provision establishing economic incentives for conducting pediatric studies. The pediatric exclusivity provision provides six months of exclusivity to be attached to any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and where the manufacturer has conducted such studies in accordance with the requirements of the provision".
2	Title: Country: Author: Date:	The Pediatric Rule [Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients] USA FDA Dec 1998 (still on US legislation website)	This regulation dated 2nd Dec 1998 consolidated several already existing CFR parts. From reference [2]: "After the passage of FDAMA, FDA finalized its regulation requiring pediatric studies for new drug and biologic applications in some circumstances (Pediatric Rule) (Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule (63 Federal Register 66632; December 2, 1998). The Pediatric Rule….effective on April 1, 1999, requires that manufacturers of certain new and marketed drugs and biological products conduct studies to provide adequate labeling for the use of these products in children. Under this regulation, FDA can require pediatric studies of a new drug or biological product if the product is likely to be used in a "substantial number of pediatric patients" or would provide a "meaningful therapeutic benefit" to pediatric patients over existing

29 http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm

	DOCUMENT		NOTES
	URL or other ref:	See footnote 30	treatments. FDA also can require pediatric studies of marketed drugs if either of these conditions applies and inadequate labeling could pose significant risks. The term "meaningful therapeutic benefit" is defined as a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population….. FDA considers the term "substantial number of patients" to mean 50,000 pediatric patients in the U.S. with the disease or condition for which the drug or biological product is indicated (63 Federal Register 66636)".
		21 CFR Parts 201, 312, 314 and 601	
	File name:	FDA CFR paed rqts for 1998.pdf	
3	Title:	Best Pharmaceuticals for Children Act	From reference [6]: "The Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted in January 2002. The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily".
	Country:	USA	
	Author:	FDA	
	Date:	2002	
	URL or other ref:	See footnote 31	
	File name:	Best Pharmls Children USA 02.docx	
4	Title:	Pediatric Research Equity Act (PREA)	From reference [6]: "PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products. Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances (see section 505B(b) of the Act). Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under section 505B(a) of the Act. Issues under section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance".
	Country:	USA	
	Author:	FDA	
	Date:	2003	
	URL or other ref:	See footnote 32	
	File name:	Ped Res equity act USA 03.docx	

30 This document is not easily retrievable via a single URL. Go to http://www.gpoaccess.gov/fr/advanced.html & do all of the following: Uncheck 2010, check 1998, check Final rules & guidelines, select On 12/02/1998, type pediatric into the search field.

31 http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm

	DOCUMENT		NOTES
5	Title: Country: Author: Date: URL or other ref: File name:	Food and Drug Administration Amendments Act [FDAAA] USA FDA 2007 See footnote 33 FDAAAct 07.docx	From reference [6]: "On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement". *Inter alia* the FDAAA reauthorizes & adds to the Pediatric Rule & the Best Pharmaceuticals for Children Acts. The American Academy of Pediatrics has published a detailed comparison of the old and new legislation.
6	Title: Country: Author: Date: URL or other ref: File name:	Protection of human Subjects: Additional Safeguards for Children in Clinical Investigations USA FDA Downloaded 080109 [original date not found] Retrieve CFR [Title 21] [Part 50] [Subpart D] via footnote34 21CFR50 pp300-303.pdf	50.51 IRB duties; 50.52 Clinical investigations not involving greater than minimal risk; 50.53 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects; 50.54 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition; 50.55 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children; 50.56 Requirements for permission by parents or guardians and for assent by children; 50.57 Wards.
GUIDANCES / RESOURCES			
7	Title:	General considerations for the clinical evaluation of drugs in infants & children	"The initial discussion pertains to factors affecting both safety & efficacy of investigational drugs in immature subjects in general. The second portion details the age specific factors which require particular consideration according to develomental state, from the fetus though 18 years of age.

32 http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ155.108

33 http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm

34 http://www.gpoaccess.gov/cfr/retrieve.html

	DOCUMENT		NOTES
	Country:	USA	Emphasis is placed on the need to elucidate unexpected toxicities which may result from immature physiologic and metabolic mechanisms, as distinct from those predictable from the drug's known pharmacological properties. Research needs are identified in terms of special techniques required to study drugs adequately in young subjects. Flexibility in approach is essential to permit the necessary modification according to the nature of the drug and its tntended use, and the age of the patient".
	Publisher:	FDA	
	Date:	Sep 1977 (still on website)	
	URL or other ref:	See footnote 35	
	File name:	FDA CTs children 1977.pdf	
8	Title:	Guidelines for the clinical evaluation of psychoactive drugs in infants & children	Provides guidance as to the various phases of clinical development of medicines for children. Preclinical studies are mentioned briefly. Pages 24-179 comprise copies of procedures for assessing psychoactive drugs & measures of effectiveness, especially in children.
	Country:	USA	
	Publisher:	FDA	
	Date:	Jul 1997 (still on website)	
	URL or other ref:	See footnote 36	
	File name:	FDA psychoactives paed 1979.pdf	
9	Title:	Draft: "General considerations for pediatric pharmacokinetic studies for drugs & biological products"	"In general, this guidance focuses on the pharmacokinetic information needed to select appropriate doses in the pediatric population, given the conclusion that the course of the disease in adult and pediatric populations is sufficiently similar to allow extrapolation of adult data to children and that dose/response relationships are also similar. The guidance does not consider (1) ways to establish safety and effectiveness of a drug in a pediatric population using either controlled or uncontrolled studies for safety or efficacy; (2) criteria to allow a determination that the course of a disease and the effects of a drug are the same in adults and the pediatric population; and (3) how to conduct pharmacodynamic studies to establish dose and/or concentration response relationships for efficacy and toxicity".
	Country:	USA	
	Publisher:	FDA	
	Date:	Nov 1998 (still on website)	
	URL or other ref:	See footnote 37	
	File name:	FDA pk studies paed 98 dft.pdf	

35 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071687.pdf
36 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072027.pdf
37 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf

	DOCUMENT		NOTES
10	Title: Country: Publisher: Date: URL or other ref: File name:	Draft: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)) USA FDA Nov 2000 See footnote 38 FDA paed rule complying with 00 dft.pdf	"This draft guidance provides recommendations for sponsors of new drug applications (NDAs) and biologics license applications (BLAs) on how to meet the requirements of the final Pediatric Rule. Areas covered include pediatric assessments, pediatric plans, waivers and deferrals, compliance issues, pediatric exclusivity, and the role of the Pediatric Advisory Subcommittee".
11	Title: Country: Publisher: Date: URL or other ref: File name:	Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling USA FDA Feb 2005 See footnote 39 FDA lactation studies dft 05.pdf	"In general, this guidance focuses on the pharmacokinetic information needed to select appropriate doses in the pediatric population, given the conclusion that the course of the disease in adult and pediatric populations is sufficiently similar to allow extrapolation of adult data to children and that dose/response relationships are also similar. The guidance does not consider (1) ways to establish safety and effectiveness of a drug in a pediatric population using either controlled or uncontrolled studies for safety or efficacy; (2) criteria to allow a determination that the course of a disease and the effects of a drug are the same in adults and the pediatric population; and (3) how to conduct pharmacodynamic studies to establish dose and/or concentration response relationships for efficacy and toxicity".
12	Title: Country: Author:	How to Comply with the Pediatric Research Equity Act USA FDA	"This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA)".

38 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072034.pdf
39 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072097.pdf

	DOCUMENT		NOTES
	Date:	Sep 2005	
	URL or other ref:	See footnote 40	
	File name:	FDA how to comply pediat res equity act 05 dft.pdf	
13	Title:	Guidance for industry: Orally inhaled & intranasal corticosteroids: Evaluation of the effects on growth in children	"This guidance provides recommendations for sponsors of orally inhaled and intranasal corticosteroids regarding the design, conduct, and evaluation of clinical studies to assess the effects of these drug products on growth. The recommendations comprise study design and efficacy and safety issues for: (1) approved drug products whose treatment effect on prepubescent growth has not been adequately characterized, and (2) potential new drug products that could be used in the treatment of allergic rhinitis and/or asthma in children. Although the recommendations in this guidance specifically apply to intranasal and orally inhaled corticosteroids, many of the recommendations can be extended to include evaluation of possible growth effects with other therapies for asthma and allergic rhinitis".
	Country:	USA	
	Publisher:	FDA	
	Date:	Mar 2007	
	URL or other ref:	See footnote 41	
	File name:	FDA children corticosteroids 2007.pdf	
14	Title:	Best Pharmaceuticals for Children Act & Pediatric Research Equity Act: Reauthorization & Improvements to Existing Law	From reference [6]: "On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement". This publication by the American Academy of Pediatrics provides a detailed comparison of the old and new legislation.
	Country:	USA	
	Author:	American academy of pediatrics	
	Date:	2007	
	URL or other ref:	See footnote 42	
	File name:	USA Best Pharmls Children_Paed Res Equity Act 07.pdf	

40 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf
41 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071968.pdf
42 http://www.aap.org/advocacy/washing/therapeutics/docs/bpcapreasidexside.pdf

	DOCUMENT		NOTES
15	Title: Country: Publisher: Date: URL or other ref: File name:	Pediatric Labeling Changes through December 24, 2009 USA FDA Dec 2009 See footnote 43 FDA paed labelling table 1209.pdf	This is a tabulation of "....key pediatric information from the studies submitted in response to pediatric legislative initiatives". "Products in this table fell within the scope of the Pediatric Rule, the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA), and contain new pediatric information. The products with PREA labeling changes which participated in the BPCA incentive program by the same sponsor are marked with an asterisk (*). The products marked with a (#) are PREA labeling changes that were not based on information from clinical trials in pediatric patients. All other labeling changes are based on information from clinical trials in pediatric patients. This list only serves to highlight information affecting the pediatric population at the time the particular application was approved resulting from the studies performed for the Pediatric Rule, BPCA and PREA".
16	Title: Country: Publisher: Date: URL or other ref: File name:	Pediatric Drug Development USA FDA Dec 2009 See footnote 44 FDA paed drug devt website 0110.docx	This file is an extract of the paediatric section of FDA's Drug Development website. Includes links to relevant legislation, pediatric exclusivity statistics, off-patent paediatric drugs, a report concerning access to new therapeutic agents for pediatric cancer, the FDA Pediatric Ethics Working Group Consensus Statement on Pediatric Advisory Subcommittee Meetings, and miscellaneous resources.
17	Title: Country: Publisher: Date: URL or other ref:	PediatricTherapeuticsResearch USA FDA Downloaded Jan 2010 See footnote 45	A list of resources concerning ethics, safety, scientific activities, international collaboration and publications relating to paediatric medicines.

43 http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf
44 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

	DOCUMENT	NOTES
	File name: FDA Paed Ther Res 0110.docx	

45 http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm

Table 5 Documents retrieved for WHO with summaries

Sorted by date

	DOCUMENT		NOTES
1	Title: Country: Publisher: Date: URL or other ref: File name:	Better medicines for children International WHO May 2007 See footnote 46 WHA Res BetterMedsChildren 07.pdf	Documentation of the World Health Assembly's resolution concerning clinical trials in children, inclusion of paediatric goals in all WHO programs, development of relevant norms & standards, adoption &/or development of paediatric-specific treatment guidelines, & general promotion of access to, and fair trade in, medicines for children that are safe, effective & of good quality .
2	Title: Country: Publisher: Date: URL or other ref: File name:	Promoting safety of medicines in children International WHO 2007 See footnote 47 Promotion_safe_med_childrens WHO 07.pdf	Outlines particular problems with medicines in children & adolescents, risk factors, legal & regulatory frameworks, the role of safety monitoring, increased risk of medication errors, & measurement & monitoring the impact of pharmacovigilance activities.
3	Title: Country: Publisher:	Sources & Prices of Selected Medicines for Children International WHO	"This publication aims to provide information about sources and prices of medicines for children. For some formulations, a number of sources are available globally, but many formulations remain challenging to source. The information given here contributes to improved access to appropriate medicines as well as indicative prices". "Besides the detailed information in the tables, the publication gives background information, methodology, analysis of the data retrieved and a discussion on a wish list for the future

46 http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R20-en.pdf
47 http://www.who.int/childmedicines/publications/en/

	DOCUMENT		NOTES
	Date:	Downloaded 261109	development of medicines for children".
	URL or other ref:	See footnote 48	
	File name:	Sources prices selected meds children WHO 09.pdf	
4	Title:	WHO Model Lists of Essential Medicines for Children	Self evident
	Country:	International	
	Publisher:	WHO	
	Date:	Downloaded 261109	
	URL or other ref:	See footnote 49	
	File name:		
5	Title:	Resources and publications	Inter alia includes text entitled *Make medicines child size*, Ten facts on children and medicines, Get involved, Accomplishments in the area so far, Clinical trials in children, Q & A, Progress reports and scientific publications, Paediatric HIV publications.
	Country:	International	
	Publisher:	WHO	
	Date:	Downloaded 261109	
	URL or other ref:	http://www.who.int/childmedicines/	
	File name:	From WHO website 1109.docx	

48 http://www.unicef.org/supply/index_47129.html

49 http://www.who.int/medicines/publications/essentialmedicines/en/index.html

Table 6 Other documents retrieved with summaries

Sorted by name of country

	DOCUMENT		NOTES
1	Title: Country: Publisher: Date: URL or other ref: File name:	Australian regulatory guidelines for prescription medicines Australia Therapeutic Goods Administration June 2004 http://tga.gov.au/pmeds/argpm.pdf From ARGPM TGA 2004.docx	Cross refers to paediatric guidelines of the EMEA. Applicants are encouraged to make paediatric formulations available and to update prescribing leaflets with information on paediatric use. Section 4.3.8 discusses products for use in special populations, including children. "Sponsors are encouraged to consider whether their products are likely to be used in children, and if so, to discuss with the TGA how to make available paediatric formulations and to update the product information document with information on paediatric use". [Cross reference to EMEA guidelines] Followed by reference to Orphan drug program (waiver of registration fees for low volume medicines) and literature-based submissions.
	Title: Country: Publisher: Date: URL or other ref: File name:	Release and Adoption of Health Canada Addendum to the ICH Guidance E11: Clinical Investigation of Medicinal Products in the Pediatric Population Canada Health Canada Dec 2003 See footnote 50 Canada paed ICH addendum 03.pdf	Discusses: 1 Additional preclinical data requirements for medicines in five classes: 1.1 Medicinal products for diseases predominantly or exclusively affecting pediatric patients (ICH E11 guidance, section 2.3.1); Medicinal products intended to treat serious or life-threatening diseases occurring in both adults and pediatric patients for which there are currently no or limited therapeutic options (ICH E11 guidance, section 2.3.2); 1.2 Medicinal products intended to treat other diseases and conditions (ICH E11 guidance, section 2.3.3); Medicinal products currently marketed for adults; Particular studies for "Biologic and biotechnology products and therapies and vaccines" (such as immunogenecity, immunotoxicity, adverse effects on cycling [young] versus quiescent [adult] cell populations in cell transplantation therapies).

50 http://www.hcsc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/e11_addendum-eng.php

	DOCUMENT		NOTES
			2 Ethics 2.1 Asserts there is an ethical imperative to conduct studies in children 2.2 States: "Studies should only be undertaken if some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent, or by other research methods. In addition, such research should either relate directly to a clinical condition occurring in the pediatric population or be of such a nature that it can only be carried out on this group of patients". 2.3 Includes observations concerning disclosure & consent
3	Title: Country: Publisher: Date: URL or other ref: File name:	Website for "Office of paediatric initiatives". Canada Health Canada Downloaded 261109 See footnote 51 Health Canada Paeds 1009.doc	An Office of paediatric initiatives was established in 2006 to deal with "…issues affecting children throughout the health prodcut life cycle, including pre-market approval & post-market surveillance & evaluation".
4	Title: Country: Publisher: Date:	 China Information from HSS/EMP/QSM/WHO Oct 2009	Advice obtained by HSS/EMP/QSM/WHO from Centre for Drug Evaluation, SFDA: There are no paediatric-specific requirements in China. However the see powerpoint presentation *Challenges of Pediatric CTs TB Drug Devt in China 0609.ppt* below which provides informal guidance.

51 http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/mhpd-dpsc/opi-bip/index_e.html

	DOCUMENT		NOTES
	URL or other ref:	Email: Potential regulatory guidelines about paediatric medicines in China	
	File name:		
5	Title:	Challenges of Pediatric Clinical Trial in TB Drug Development in China	*Inter alia* this powerpoint presentation outlines regulatory requirements for pediatric clinical studies in China. For drugs approved overseas but not approved in China - With indication for both adult and children based on complete foreign adult/pediatric clinical data, only adult clinical study is required in China. The market approval will be granted for both adult and children based on China adult data - With indication for children only, pediatric clinical study in China will be required. For innovative drug intended for use in children - The clinical requirements are not more than FDA's - The domestic sponsor tends to complete majority of all clinical studies (even all) in adult, before considers to develop the use in pediatric population. - The same recommendation has been raised by principal investigators.
	Country:	China	
	Publisher:	Yajie Li, Senior reviewer, SFDA, China	
	Date:	2009	
	URL or other ref:		
	File name:	Challenges of Pediatric CTs TB Drug Devt in China 0609.ppt	
6	Title:	Clinical investigation of medicinal products in the pediatric population" ICH-E11	"It is the goal of this guidance to encourage and facilitate timely pediatric medicinal product development internationally. The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population."
	Country:	EU, Japan, USA	
	Source:	ICH	
	Date:	Jul 2007	
	URL or other ref:	See footnote 52	
	File name:	ICH paed clin gs aka E11 00.pdf	

52 http://www.ich.org/LOB/media/MEDIA487.pdf

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7	Title: Country: Publisher: Date: URL or other ref: File name:	Information in English on Japan regulatory affairs, English Regulatory Information Task Force Japan Japan Pharmaceutical Manufacturers Association Mar 2008 See footnote 53 Japan reg gs JPMA 08 full text.pdf	"At present, laws and regulations aimed at drug development and direct promotion of information dissemination in the pediatric field such as those in the EU and United States do not exist in Japan. When clinical trials are planned for dose setting, etc. in children during approval applications or after approval of drugs intended for use in children to collect information on experience of use in pediatric populations, the reexamination period can be now extended for a set period not exceeding 10 years in consideration of special surveys and clinical studies during the reexamination period". "A Study Group on Unapproved Drugs was founded in December 2004 to perform reliable clinical studies on drugs not approved in Japan for which efficacy was established and approvals granted in the West in order to assure prompt approvals in Japan. Periodic surveys and scientific evaluations of requests of academic societies and patients are undertaken, often involving drugs for pediatric use. In March 2006, a Study Group on Pediatric Drug Treatment was established to collect and evaluate evidence on the efficacy and safety of pediatric drug treatment, to conduct surveys on prescriptions for drugs for pediatric use and to provide information to health professionals for the environmental improvement to adequate pediatric drug treatment. PMDA consultations include those on clinical development in pediatric populations and development of products for pediatric use". A Guidance on Clinical studies on Drugs in Pediatric Populations is said to have been issued [no translation was found on the internet, & this guideline was not found on the English version of the DRA's website].
8	Title: Country: Publisher: Date: URL or other ref: File name:	Paediatric medicinal products Netherlands Medicines Evaluation Board July 2007 http://www.cbg-meb.nl/CBG/en/ Neths_info from website 1109.docx	A "Consultative paediatricians group" (aka "Pediatricians' Sounding-Board Group") was established by the MEB as of 1 Feb 2006". Its functions include: No papers were identified on the MEB website from the Pediatricians' Sounding-Board Group. Articles 7 & 8 of the EU Paediatrics Regulation were implemented as of 26/7/08 and 26/1/09 respectively.

53 http://www.jpma.or.jp/english/parj/0903.html

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9	Title: Country: Publisher: Date: URL or other ref: File name:	 Switzerland Email from Swiss Medic Nov 2009 Email SwissMedic 211009.docx	"In general for medicines that are predominantly used in children, a marketing authorisation application with only adult data that is without paediatric data is not acceptable. In our guideline for the SPC we insist on a clear statement on use in paediatrics in the rubric dosing. In general registration of paediatric medicines follows the same rules as for adults. There are the same requirements. for special contexts we relate to international guidelines such as the EMEA guideline paediatric pharmacology, which you can find on the EMEA website. At present there is not yet a legal basis to enforce paediatric development in Switzerland."
10	Title: Country: Publisher: Date: URL or other ref: File name:	From Swiss Medic website Switzerland Swiss Medic Downloaded 021009 See footnote 54 SwissMedic paed gs website.docx	A list of documents that are available only in German or French
11	Title: Country: Publisher: Date: URL or other ref: File name:	Medical research involving children UK Medical Research Council 2004 See footnote 55 Med Res Involving Children MRC UK 04.pdf	Topics: Why do we need research involving children? What has limited research so far, and what are the challenges? The way forward – ethical considerations. Children, ethics and the law

54 http://www.swissmedic.ch/zulassungen/00171/00180/ index.html?lang=en
55 http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430

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12	Title: Country: Publisher: Date: URL or other ref: File name:	MHRA/Department of health strategy on medicines for children UK MHRA July 2004 See footnote 56 paediatricstrategy MHRA 0704 .pdf	Short term: - When the US FDA has published paediatric exclusivity grants, ask UK Marketing Authorisation Holders for copies of relevant data - Provision of scientific advice without charge and fee waivers for applications to include paediatric safety information in the SPC. - Consider extending fee waivers to all paediatric specific applications, where they are in the public health interest. - Encourage EU PIPs (see Table 3 Row 23) Medium term: - When companies signal an intention to discontinue medicines for which there is a paediatric therapeutic need, encourage continued availability. - Identify needed paediatric medicines that are licensed outside the UK & invite the companies to submit applications for authorization, focusing on medicines authorised elsewhere in the EU. - Explore direct actions which may be taken to standardise the quality of extemporaneous formulations for paediatric use - Encourage development of paediatric formulations of off-patent & on-patent medicines, focussing on a priority list - Establish a short priority list of paediatric medicines for the UK - Take a leading role in preparing European guidance on topics relating to paediatric drug development - Developing detailed plans, in discussion with stakeholders, for a managed - Develop a managed clinical research network for medicines for children, providing the NHS infrastructure for research in this area. Infrastructure support will be strengthened & funding will be set aside for this purpose. The Research & Development Directorate of the DoH is developing detailed plans. - The UK DoH will support the distribution of the BNF-C to health care professionals. - MHRA will work towards improving paediatric specific information in product information leaflets.

56 http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON009667&RevisionSelectionMethod=Latest&noSaveAs=0&Rendition=WEB

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		Long term: - The EU Regulation on paediatric medicines will be supported whilst: • striking the right balance of costs & benefits for the UK's NHS and for the pharmaceutical industry, & achieving provisions that are practical & workable, & do not create problems for existing UK arrangements.
13	Title: Medicines for children Country: UK Publisher: MHRA Date: Last available update 140307 URL or other ref: See footnote 57 File name: MHRA website paeds 07.doc	MHRA website
14	Title: MHRA exercise to update SmPCs following EU paediatric work-sharing procedures Country: UK Publisher: MHRA Date: Last update 120110 URL or other ref: See footnote 58	Implementation of the EU Pediatric Rule in the UK via updates to SmPCs.

57 http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON009648&ssTargetNodeId=836&DynamicListQuery=&DynamicListSortBy=xCreationDate&DynamicListSortOrder=Desc&DynamicListTitle=&PageNumber=null&Title=Medicines%20for%20children&ResultCount=10

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	File name:	Meds for children MHRA update SmPCs 0110.docx	
	Title: Country: Publisher: Date: URL or other ref: File name:	Pediatrics: An informal note Ukraine Email from a Ukrainian contact via WHO Regional Office for Europe 091009 Paediatrics_WHO_Ukraine_amended 091009.doc	There is a requirement as to labelling of medicinal products for use in the pediatric population, including an indication of the age group of patients. The State Pharmacological Center approves CT protocols involving pediatric populations. ADR data include results for children. Amendments to Civil Code of Ukraine concerning regulation of CTs in minors were developed but not approved. Lack of key paediatric medicines affects significantly the quality of medical aid for children. "Order 13.02.2006 No36 concerning clinical trials includes an item concerning clinical trials in minors. The Ukrainian state formulary of medicinal products (2009) has a section entitled "Neonatalogy" which includes 92 medicines. The national list of essential medicines includes 149 paediatric medicines. If a foreign applicant for registration has paediatric strengths or dosage forms of a medicine [presumably meaning marketed elsewhere], paediatric indications may not be claimed unless the paediatric strengths or dosage forms are registered in Ukraine".

58 http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/Whatsnew/CON031043

Table 7 Abbreviations used in this report

ARGPM	australian regulatory guidelines for prescription medicines
BLA	biologics license application (USA)
BPCA	Best Pharmaceuticals for Children Act (USA)
CDE	center for drug evaluation (China - part of SFDA)
CFR	code of federal regulations (USA)
CT(s)	clinical trial(s)
DRA	drug regulatory authority
EC	european commission
EMA	european medicines agency (current name)
EMEA	european agency for the evaluation of medicinal products (old name)
EU	european union
FDA	food & drug administration (USA)
FDAAA	food & drug administration amendments act (USA)
FDAMA	food & drug administration modernization act (USA)
HHS	health & human services (USA)
ICH	international conference on harmonization
JPMA	japan pharmaceutical manufacturers association
MEB	medicines evaluation board (Netherlands)
MHRA	medicines & healthcare products regulatory agency (UK)
MPA	medical products agency (Sweden)
MRC	medical research council (UK)
NCE	new chemical entity
NDA	new drug application (USA)
NDRA	national drug regulatory authority (a WHO term)
NIH	national institutes of health (USA)
PDCO	paediatric committee (EU)
PIP	paediatric investigation plan (EU)
PMSB	pharmaceutical & medical safety bureau (Japan)
PREA	pediatric research equity act (USA)
PUMA	paediatric-use marketing authorisation (EU)
SFDA	state food & drug administration (China)
SmPC (or SPC)	summary of product characteristics (EMEA)
TGA	therapeutic goods administration (Australia)
WHA	world health assembly
WHO	world health organisation

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6. FDA. How to Comply with the Pediatric Research Equity Act. US National archives & records administration; 2005.