The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

Sodium Valproate Timeline – Key Events

Working Draft – April 2020

This document is a working paper of the Independent Medicines and Medical Devices Safety Review. It lists key events in the history of sodium valproate use in pregnancy, drawing on evidence that the Review has received in writing, at the oral hearings, in meetings with the patient groups, and our own research. After further review, final versions will be published at the same time as the Review's report.

Disclaimer

The statements made and the opinions expressed in the components of the timeline do not purport to reflect the opinions, views or conclusions of the Independent Medicines and Medical Devices Safety Review's ('IMMDSR). The statements and opinions made do not imply the expression of any opinion whatsoever on the part of the IMMSDR concerning the truthfulness, veracity, accuracy or legal status of any statements or opinions made and published on the IMMDSR website. Nor does the IMMSDR accept any legal liability arising from any statements or opinions so expressed and published.

Key

Evidence Source/Action taken by	Colour
Regulatory/public bodies	
Manufacturers	
Key Studies	
Patient Groups and Charities	
Media	
International/devolved administrations	
Significant Events	
Parliamentary Activity	

Timeline

Year	**Source**	Evidence/Action taken
1882		Valproic acid (also known as dipropylacetic acid) synthesised for use as a laboratory solvent by Burton.[1]
1963		Discovery of the anti-epileptic properties of valproic acid in France.[2]
1967	Sanofi written evidence	Sodium valproate initially licensed in France with the approved therapeutic indications of: (a) generalised or focalised epilepsies and (b) personality or character disorders linked to epilepsy.
1969 - 1973	Sanofi written evidence	Sodium valproate supply supplied in Belgium, Holland, Luxembourg, West Germany and Spain, through a licensing agreement with Belgian company, Labaz.
1969	Sanofi written evidence	Further clinical trials carried out in the UK confirmed that sodium valproate was effective in reducing the incidence of seizures in patients with petit mal, grand mal, myoclonic and akinetic epilepsy and photosensitive epilepsy, including in patients with long standing epilepsy that had proved refractory to other therapies.
1960s and 70s	Published articles	A number of letters and papers were published around this period drawing attention to concerns about the teratogenicity of all anti-epileptic (or anti-convulsant) drugs.[3]

[1] *Burton BS (1882) On the propyl derivatives and decomposition products of ethylacetoacetate. Am Chem J3: 385–395 in: Löscher W (1999) The discovery of valproate.* In: Löscher W (eds) Valproate. Milestones in Drug Therapy. Birkhäuser, Basel

[2] Shorvon, SD. Drug treatment of epilepsy in the century of the ILAE: The second 50 years, 1959–2009. Epilepsia 50(s3): 93-130

[3] For example, the following have been shared with the Review:
1963 – Lawrence, A. Anti-epileptic drugs and the foetus. British Medical Journal 1973; 16; p267.
1964 - Janz, D and Fuchs, U. Are anti-epileptic drugs harmful during pregnancy? Dtsch Med Wochenschr 89: 241-248.
1968 – Meadow, SR. Anticonvulsant drugs and congenital abnormalities. Lancet 2(7581): 1296.
1973 – Lowe, CR. Congenital malformations among infants born to epileptic women. The Lancet. Jan 6:p9-10.

1971	MHRA written evidence	Application for sodium valproate license received.
1 Sept 1971		Medicines Act 1968 comes into force.
Jan 1972	MHRA written evidence	Committee on Safety of Medicines (CSM) – Sub-Committee on Toxicity and Clinical Trials *'recommends that decision on Labazene should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate… Further toxicological and teratological data is also required.'* CSM - Main Committee agreed, and decided that '*Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.'*[4] A Medicines Commission paper notes that the clinical trial data provided with the Product License application was carried out in a patient sample which differed from the majority of the United Kingdom in its genetic composition, dietary intake, and other concomitant drug intake.[5]
May 1972	MHRA written evidence	CSM – Sub-Committee on Toxicity and Clinical Trials *'On the evidence before them the Sub-Committee are unable to advise the grant of product licences for these preparations for the purposes indicated in the application since the animal toxicology, including teratology provided is inadequate, and the data which has been presented gives ground for concern in view of the expected long term administration of the drug.'*[6]
June 1972	MHRA written evidence	The following month, the CSM Sub-Committee on Toxicity and Clinical Trials stated in reference to Labazene tablets:

1973 – Fedrick, J. Epilepsy and Pregnancy: a report from the Oxford record linkage study. British Medical Journal 1973; 2:p442-448.
1974 – Hill, R et al. Infants Exposed In Utero to Antiepileptic Drugs: A Prospective Study. The first prospective study to investigate this issue.
1974- Barr, M et al. Digital hypoplasia and anticonvulsants during gestation: a teratogenic syndrome. The Journal of Pediatrics 1974; 84(2):p254-256.
1975- Hanson, JW and Smith, DW. The fetal hydantoin syndrome. The Journal of Pediatrics 1978; 307: p285-290.
[4] MHRA – minutes in annex, 'A CSM Minutes January 1972'
[5] MHRA supplementary evidence – Medicines Commission MC 76/112 A 'A Note on Epilim – Sodium Valproate'
[6] MHRA – minutes in annex, 'A CSM Minutes June 1972'

		'On the evidence before them the Sub-Committee recommend the grant of a product licence for one year for this preparation for the purposes indicated in the application provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy, and subject to all patients being monitored for therapeutic efficacy and safety' In reference to the Labazene solution, the Sub-Committee recommended: '*that a decision on this product should be deferred pending the outcome of discussions between the Sub-Committee on Chemistry and Pharmacy and the applicant on the question of the "dropper" for use with this preparation.'* The Main Committee agreed regarding the tablets, and also advised that the product '*should be regarded as new for the purpose of a special directive for the reporting of adverse reactions.'* The document notes that the applicant did not wish to proceed further with the Solution.
Aug 1972	Sanofi and MHRA written evidence	Conditional product licence granted for sodium valproate 200mg plain tablets, under the brand name "Labazene" (changed to "Epilim" in March 1973) to Pharmacy Products (UK) Limited, a joint venture between Labaz Group and Reckitt & Colman ("R&C"). Due to the animal data suggesting a possible risk of birth defects, the CSM advised a license should only be granted for one year, limited to hospitals and other centres specialising in the treatment of epilepsy. The licence was subject to the condition that all patients would be monitored for efficacy and safety and the results reported to the licensing authority in writing at six months and, again, at ten months after grant of the licence.[7]
Oct 1972	Published article	*Speidel and Meadow*[8] - retrospective survey of the outcome of 427 pregnancies in 186 women with epilepsy, showed that major congenital malformations occurred with twice the expected frequency compared to children in the control group. Developmental delay was also found to be higher in the children born to mothers with epilepsy. The authors suggest '*the malformations probably have a multifactorial aetiology, and, while anticonvulsant drugs may have a teratogenic action…, such teratogenic activity is likely to be influenced by hereditary and environmental factors.'* They also emphasised the need for folate supplementation.

[7] MHRA - minutes in annex, "A CSM Minutes January 1972", 'A CSM Minutes May 1972' and 'A CSM Minutes June 1972', A CPS minutes January 1972)
[8] Speidel, BD and Meadow, SR. Maternal epilepsy and abnormalities of the fetus and newborn. The Lancet 1972: 7782: 839-43

		An editorial in the same issue of The Lancet[9] stated that '*the case implicating anticonvulsant drugs is suggestive but unproven*', noting their teratogenicity in animal studies, and a suggested mechanism via folate deficiency. Given the important role of these drugs in women with epilepsy, the editorial suggested that this finding should be regarded as a stimulus for further research and not general alarm.
1 Jan 1973		UK joined the EEC. Under European drug regulatory regime
Mar 1973	Sanofi	Commencement of supply of Epilim in the UK
Apr – Sep 1973	MHRA written evidence, minutes of CSM and CSM/AR	The Committee for the Safety of Medicines, and the Sub-Committee on Adverse Reactions[10] 24th April 1973 Letter from Imperial Chemical Industries Limited to the Sub-Committee on Adverse Reactions, requesting a modification to the Data Sheet for 'Mysoline' (Primidone, an anticonvulsant), to include the wording: '*There is some evidence of a higher than average incidence of congenital abnormalities in infants born of epileptic mothers. The precise factors influencing this are unknown, but the possibility that anticonvulsant therapy may be involved and the very slight risk of an abnormal foetus must be weighed against the risks of withholding treatment during pregnancy.'* The secretary of the Sub-Committee on Adverse Reactions suggested that the Committee may wish to consider whether data sheets of other anticonvulsants should include similar information. 16 May 1973 (CSM/AR) Minutes state that the Sub-Committee on Adverse Reactions welcomed the action of the manufacturer ICI Ltd regarding Mysoline, and recommended that the licensing authority should be advised to require that a similar statement is included in all data sheets for anticonvulsants.

[9] Are Anticonvulsants Teratogenetic? The Lancet 1972 7782: 863-864
[10] BN 116/17 CSM/AR/1/73 Committee on Safety of Medicines. Sub-Committee on Adverse Reactions. Meetings 17.1.1973-21.11.1973. National Archives.; also see written evidence provided by MHRA: Minutes of the Committee on Safety of Medicines.

		May 1973 CSM Annual Letter to Doctors[11] On the subject of anticonvulsants, it states '*Meanwhile it is now clear from other studies that the use of anti-convulsants during pregnancy (including phenobarbitone and Promodone as well as Phenytoin, singly or in combination) is liable to produce other abnormalities as well as harelip and cleft-palate. The risk appears to be low and not sufficient to justify stopping the use of anti-convulsants when they are necessary for the control of epilepsy.'* 28 June 1973 (CSM) Minutes of the Main Committee state that they also welcomed the action by ICI Ltd, but '*did not however think that the evidence was as yet sufficiently conclusive for the inclusion of such a statement to be advised as a general condition in association with the licensing of all anticonvulsant preparations.'* 18 July 1973 (CSM/AR) Minutes of this meeting note the above, comment further that the Main Committee '*had thought the evidence not sufficiently conclusive to require all other manufacturers of anticonvulsant products to use a similar statement, especially as it could give rise to fruitless anxiety. The Sub-Committee believed, however, that the character of the evidence was strong enough for an assurance to be given to the Main Committee on that account, but accepted the point regarding anxiety. Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that proposed by ICI could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients seeing it.'* 26 July 1973 (CSM) Minutes from the Main Committee also state that: '*As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard..'* 30 August 1973 (CSM) '*The Chairman reminded the main Committee of the Sub-Committee's recommendation that all anticonvulsants should have an associated warning regarding possible teratogenicity. The Committee's views regarding the difficulties this presented had been conveyed to the Sub-Committee but they still felt the evidence sufficiently strong to call for some action on the matter.*' It was discussed that

		the Sub-Committee's report on congenital abnormalities could draw attention to this risk. In addition, the Chairman stated he had agreed to discuss how earlier publicity could be achieved with the BMA '*with a view to ensuring that all doctors were alerted to the hazards, yet without creating undue alarm.'* 19 September 1973 (CSM/AR) Minutes state that the Main Committee had further considered the question of the warning, and were not opposed '*but in practice it would be difficult to identify all manufacturers of drugs used for epilepsy.'* The Main Committee suggested that the broader report on teratogenicity could be used to publicise anticonvulsant teratogenicity. The Sub-Committee felt that further warnings to the profession were necessary, through the BMJ and a letter from the Chairmen to all doctors.
Sept 1973	Sanofi written evidence	Application for full product licence in the UK submitted to DHSS by Pharmacy Products (UK) Limited. This application described that a study in rats and mice demonstrated teratological effects at high doses (doses toxic to the mother), but not at doses recommended for humans. R&C advised DHSS that valproate had been marketed in five European countries for up to 4 years, but no reports of congenital abnormalities had been reported.
Feb 1974	MHRA written evidence	The CSM met with the BMA to discuss how to draw doctors' attention to the teratogenicity of anti-convulsants. '*They all felt it was important to avoid causing panic amongst patients with epilepsy and inducing doctors to withdraw anti-convulsant therapy because it was clear that the hazards associated with their continued use were less that those associated in their withdrawal.'*[12]
March - Aug 1974	MHRA written evidence	CSM Minutes 28 March 1974[13] The Sub-Committee on Toxicity and Clinical Trials had considered further reports submitted following the limited licence initially granted for sodium valproate, and made the following recommendations. (a) Under "Uses" the licence shall read: *"For use in generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or those resistant to other treatment".*

[11] Referred to in MHRA supplementary evidence. Medicines Commission. MC 76/112A 'A Note on Epilim – Sodium Valproate'
[12] MHRA supplementary evidence. Medicines Commission MC 76/112A 'A Note on Epilim – Sodium Valproate'
[13] MHRA – minutes in annex, C Minutes of CSM March 1974

		(b) The following warning shall be included in all literature (data sheets, journal advertisements, representative hand-outs and medical mailings) issued about the product: *"Women of childbearing age* *This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings."* CSM Minutes 22 August 1974[14] Minutes of this meeting state that the committee had considered a request in March of 1974 to remove the monitored release restriction, and that this could be allowed on conditions set out by the Sub-Committee on Toxicity and Clinical Trials. Additionally, '*Before proceedings with the variation, officials had sought the views of the Minister of State (Health) in view of the concern regarding the availability of drugs which could harm the foetus. On the understanding [that] on the basis of animal studies, the teratogenic effects of Epilim were of the same order as phenytoin, the Minister agreed to the variation.'* In the same meeting, the use of (all) anticonvulsants in pregnancy were further discussed. The Main Committee agreed that the views of the Sub-Committee on Adverse Reactions should be sought on whether further warnings were required. Additionally, it was noted that manufacturers of anti-convulsant preparations containing phenytoin and phenobarbitone had been asked (if not already included) to insert the following warning in the data sheets: '*There is some evidence that anti-convulsant medicines can cause foetal abnormalities and care is needed in their use during the early months of pregnancy. The physician must consider the relative hazards to both mother and foetus associated with the withdrawal or reduction of anti-convulsant therapy and of continuing therapy with the possibility of inducing congenital malformations.'*

[14] MHRA - minutes in annex, C Minutes of CSM August 1974

28 Oct 1974	MHRA/Sanofi written evidence	CSM Minutes from September 1974[15] report that the applicant found the conditions acceptable. A full licence for sodium valproate was issued for five years, backdated to 2 August 1973. The licence was subject to conditions reflecting the teratogenic effects in animals, including inclusion of specific warnings in data sheets and materials promoting the product to doctors (as described above).
1975	Published article	Symposium on Sodium Valproate held at Nottingham University 23-24th September 1975, on behalf of Reckitt-Labaz. Guy's Hospital Gazette[16] stated: *'The drug had been released with the warning that it has been shown to be teratogenic in animals. Very few women in this country have been taking this drug during pregnancy, and the data on their offspring is inadequate. Many more women on the continent have presumably had pregnancies while taking the drug, but unfortunately statistical data on the instance of fetal abnormalities were not available.* *With the memory of thalidomide, few clinicians would be happy to allow their female patients to take sodium valproate at the time of pregnancy risk or during pregnancy until this point has been clarified.'*
Jan 1975	Ireland	Sodium valproate licenced for use in Ireland
Apr 1975	Published article	*Drug and Therapeutics Bulletin* on 'Anticonvulsants in Pregnancy'.[17] This information for doctors stated that regular anticonvulsant therapy should not be altered during pregnancy, although considered that specialists may choose to reduce or remove the dose prior to pregnancy in women who are no longer having fits. It advised that women are given iron and folate supplements throughout pregnancy as they have an increased chance of developing anaemia. The bulletin includes a summary of the current research on congenital abnormalities in the offspring of women with epilepsy, and suggests that teratogenic effect of the drugs are probably responsible for the increased incidence in this population, although the epilepsy itself may be a factor.
Nov 1975	Published article	*Simon and Penry*[18] - Review of literature confirmed effectiveness of valproate.

[15] MHRA - minutes in annex, C Minutes of the CSM September 1974
[16] Hughes, RAC. Sodium Valproate – A New Anticonvulsant. Guy's Hospital Gazette New Series Vol. XC. 90(2254):8-10 31 January 1976.
[17] Anticonvulsants in pregnancy. Drug and Therapeutics Bulletin. April 1975 13(9):33-35
[18] Simon, D and Penry, JK. Sodium Di-*N*-Propylacetate (DPA) in the Treatment of Epilepsy:A Review. Epilepsia 1975: 16: 549-573. doi:10.1111/j.1528-1157.1975.tb04738.x

Dec 1975	Published article	*Drug Therapeutics Bulletin* on Sodium valproate[19] summarised the clinical trials which had taken place to date: in most trials it was added to the existing drug regimen, no trials gave patients sodium valproate alone, double-blind or for long periods. However addition of sodium valproate appeared to have beneficial effect in intractable epilepsy, although its effectiveness in different epilepsy types was not clear. The bulletin also noted unwanted effects: '*Some evidence of teratogenicity has been found in animals, but it is not known how great this risk is in pregnant women and whether it is likely to be more or less than for other anti-epileptic drugs. Whether there is a risk of malformation in the offspring of men taking the drug is unknown.'* The article concluded that sodium valproate is worth giving as an additional drug in patients who have not had adequate outcomes from other drugs, however it cannot be recommended as the drug of first choice until it has been more fully evaluated.
1976	Published article	*Whittle*[20] demonstrated the teratogenicity of sodium valproate in rabbits, rats and mice when given in large doses; this was also demonstrated by *Brown et al* in[21] 1980.
1976	MHRA written evidence	The Medicines Commission paper, 'A note on Epilim'[22] set out the recent history (see timeline above), and the legal position and decision-making around licensing, and pointed out that the balance of risk and therapeutic advantage is difficult. It noted: '*Had there been a category of drugs whose prescribing was restricted to specialists in the treatment of the particular disease, it is clear that Epilim would have been included in this category, at least initially until its place in the treatment of epilepsy had been assessed.*' In addition, it described the concern about the difficulties in controlling the promotion of sodium valproate, and in particular a letter from a Company which '*…made no mention of the teratogenicity of Epilim, merely relying on the data sheet which it enclosed, but did state that "Epilim represents an advance on traditional therapies, in offering effective control of seizures, as well as the virtual absence of unacceptable side effects".'*

[19] Sodium valproate and clonazepam for epilepsy. Drug and Therapeutics Bulletin Dec 1975 13(25):97-98
[20] Whittle BA. Preclinical teratological studies on sodium valproate (Epilim) and other anticonvulsants. In: Legg NJ, ed. Clinical and pharmacological aspects of sodium valproate (Epilim) in the treatment of epilepsy Tunbridge Wells: MCS Consultants, 1976: 105-10
[21] Brown NA, Kao J, Fabro S. Teratogenic potential of valproic acid. The Lancet 1980; i: 660-61
[22] MHRA supplementary evidence. Medicines Commission MC 76/112A 'A Note on Epilim – Sodium Valproate'

1977	Published article	Pinder et al[23] - This review paper set out contemporary understanding of the efficacy and side effects of sodium valproate, noting that at that point there were few controlled trials of sodium valproate in the treatment of epilepsy. The review set out in a few places information regarding pregnancy, but also noted that at the time there were only 8 published reports of mothers coming to term while on sodium valproate, none of which showed congenital abnormalities. *'Sodium valproate, like certain other antiepileptic drugs, produces dysmorphogenic effects in animals. This possible hazard must be weighed against the benefits, if the drug is to be given to women of child-bearing age. It should probably be used only in severe cases of epilepsy or in those who are resistant to other treatment, though this is a matter for individual clinical judgement.'*
Nov 1977	National Archives	A Working Party on Anticonvulsant Drugs set up by the Medical Research Council met on 17 November 1977, '*to make recommendations about the possibility of mounting trials to investigate the long-term effects of anticonvulsant drugs with particular reference to drug interaction and behaviour*'.[24] A paper considered at the Working Party meeting suggested further animal studies into the method of action of teratogenicity of antiepileptic drugs.[25] The Working Party report noted that there '*was a great need for careful long-term toxicity studies of drugs in current use'*, and recommended that applications for trials considering the long-term effects should be sympathetically considered, and that a Co-ordinating Group should be set up with the aim of improving exchange of knowledge between clinical and basic researchers.[26] It expressed concern that '*it was still not certain how well [sodium valproate] compared with other drugs currently in use'*, again without specific reference to teratogenicity.
1977-1988	Sanofi written evidence	Sanofi and Abbott conducted genetic toxicology studies in relation to valproate during this period. Sanofi report that the results of all these studies were negative and no genotoxic potential for valproate was identified.

[23] Pinder, RM et al. Sodium Valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy. Drugs 1977 13: 81-123 doi: 10.2165/00003495-197713020-00001
[24] Medical Research Council Circulation. Neurosciences Board: MRC Working Party on Anticonvulsant Drugs. Final Report. March 1978. FD 23/2660 National Archives
[25] Richens, A. Outline proposal for the Medical Research Council on Adverse Effects of Antiepileptic Drugs. AC 77/6. Paper for the MRC Working Party on Anticonvulsant Drugs 17 November 1977.
[26] Medical Research Council Circulation. Neurosciences Board: MRC Working Party on Anticonvulsant Drugs. Final Report. March 1978. FD 23/2660 National Archives

Feb 1978	FDA (USA); see references	Abbott were granted a licence to market valproic acid in the US under the brand name Depakene.[27] The process of licencing had taken 8 years due to requests for further research, including animal studies, dosage studies and controlled trials in humans. Frustrations with this process had been aired at a Workshop the previous year,[28] which drew attention to existing international studies (p61), as well as the need for better treatment for patients with epilepsy. Following a discussion about the difficulty of ascertaining teratogenic effects in a matter of years (highlighting that it took 40 years for the teratogenic effects of phenytoin to be recognised), the workshop also drew attention to the pregnancy forms collected by Reckitt and Colman in the UK (p72). Additionally the workshop papers mention the 'pragmatic' approach of licensing in the UK (p980), which considered available French data, and did not require clinical trials ('the usual procedure for authorization of a non-British Product'), on which basis a limited licence was granted for marketing in hospitals only.
Sept 1978	Published article	*Addy*[29] - Presented a scheme for the drug treatment of childhood epilepsy, and discussed the evidence for efficacy and side effects of the anti-epileptic drugs (AEDs) on the market at that time (older medicines phenobarbitone and primidone, and the newer carbamazepine and sodium valproate). The paper describes sodium valproate as '*having been greeted by some as the greatest thing since Greta Garbo'*, and notes that so far, it '*has shown remarkably little toxicity'*.

[27] The Food and Drug Administration's Process for Approving New Drugs. Hearings before the subcommittee on science, research and technology of the committee on Science and Technology. US House of Representatives. Ninety-Sixth Congress. First session. June 19, 21; July 11, 1979 [No 37] Available online: https://babel.hathitrust.org/cgi/pt?id=mdp.39015081270806

[28] US Department of Health, Education and Welfare . Workshop of Antiepileptic Drug Development. April 15, 1977, Arlington, Virginia. Edited Transcript.

[29] Addy, DP (1978) Childhood epilepsy. British medical Journal 2:811-812 doi: 10.1136/bmj.2.6140.811

1980	MHRA written evidence	CSM considered a proposal for a study on drugs and congenital malformations.[30] This had been raised in the context of Debendox.[31] DHSS were unable to fund the study, and the Adverse Reactions sub-committee had considered other ways of carrying out this research. While the Main Committee agreed this was a desirable investigation, it was agreed that the matter was deferred pending consideration of the question of funding.
March 1980	Published article	*Brown et al.*[32] - Letter to the Lancet highlighting their concerns about the teratogenicity of valproic acid, arising from their animal data which suggested that valproic acid is a more potent teratogen than phenytoin (a weak human teratogen) and as potent as trimethadione (a powerful human teratogen). They stated they do not want to '*raise unjustified doubts about a useful drug*' and are looking for more information, as published clinical data at that point did not show a relation between valproic acid and human malformations. They ask their colleagues to contact them with any further information on valproic acid use in early pregnancy.
April 1980	Published article	*Hiilesmaa et al.*[33] – An update on a prospective study carried out in Finland. At this early stage they note that their series is too small to justify conclusions about the teratogenic potential of valproic acid, but '*absence of any anomalies in the offspring so far has encouraged us to allow at least two groups of patients to continue valproic acid during pregnancy - namely, women who are already pregnant and are taking the drug, since in most of such cases it would be too late to prevent teratogenesis, and in women for whom valproic acid was considered essential for the control of seizures before they became pregnant.*'
Aug 1980	Published article	*Dalens et al.*[34] – Case report of female infant exposed to valproate throughout gestation. The infant had a number of physical malformations and died after 19 days. The authors suspected a causal link between valproate use and these physical abnormalities.

[30] MHRA evidence. Annex D – CSM Minutes 1980.
[31] A combined preparation of doxylamine, dicycloamine and pyridoxine used to treat nausea and vomiting early in pregnancy, marketed in 1956 in the US as Bendectin and 1958 in the UK as Debendox. There were anecdotal reports of congenital malformations in the offspring of women who had taken this drug during pregnancy, although studies failed to show evidence of a connection. Production was halted in 1983, and the manufacturers settled a group legal case out of court in the US. (*Source: M L'E Orme (1985) The Debendox Saga. BMJ (Clin Res Ed) 291: 918-9 doi:10.1136/bmj.291.6500.918*)
[32] http://www.sciencedirect.com/science/article/pii/S0140673680911599
[33] Hiilesmaa, VK et al. Valproic acid during pregnancy. The Lancet 1980: **315**(8173): 883.
[34] Dalens, B et al. Teratogenicity of valproic acid. J Pediatr 1980: 97, 332-333

Dec 1980	Published article	*Nakane et al.*[35] - Multi-institutional collaborative study in Japan reported that teratogenicity of anti-epileptic drugs was not high, but should nevertheless be conservatively prescribed in pregnant patients. The drugs which caused significant teratology included: trimethadione, phenobarbital, primidone, pheneturide, acetazolamide, and mephobarbital. In this study, diphenylhydantoin, carbamazepine and sodium valproate failed to reach significant levels.
1981	Sanofi	Sanofi acquired the Labaz Group. At that time, three formulations of Epilim were licenced in the UK: Epilim Plain Tablets 200mg, Epilim Enteric Coated (200mg and 500mg) and Epilim Syrup. The data sheets at this point contain the warnings about animal teratogenicity and limitations of use in women of child-bearing age.
March 1981	Published article	*Gomez*[36] - Case report of male infant exposed to valproic acid, clonazepam and phenobarbital in utero. The infant was born with a neural tube defect and minor abnormalities to the feet. The clinician asks for any of observations of teratogenic effects of valproate to be shared.
March 1981	BNF	BNF No. 1 contained the following information: '4.8 Antiepileptics 4.8.1 Control of Epilepsy *Pregnancy* Although several antiepileptics are teratogenic in *animals*, the increased risk of congenital malformations is in practice slight. Abrupt withdrawal of antiepileptics also carries risk of increased seizure frequency or status epilepticus.' Sodium Valproate was at that time the drug of first choice in the treatment of some epilepsies.[37]

[35] Nakane et al. Multi-institutional study on the teratogenicity and foetal toxicity of antiepileptic drugs: A report of a collaborative study group in Japan. Epilepsia 1980; 21: 663-680
[36] Gomez, MR. Possible teratogenicity of valproic acid. Journal of Pediatrics 98(3):508 March 1981
[37] NHS Resolution written evidence to the Review

Aug 1981	Published article	An article in the British Medical Journal (the 'BMJ') concluded: *'…on balance, although phenytoin and other antiepileptic drugs appear to carry a teratogenic risk, it does not justify (with the exception of the diones) discouraging a women who needs anticonvulsant treatment from having a child or changing a satisfactory drug regimen when the epilepsy is well controlled. Doctors should explain to parents that the increased risk is small and that many of the complications are minor or remediable……Until further facts about the teratogenic risks of antiepileptic drugs are known, their various other side effects also need to be considered, and on balance carbamazepine or sodium valproate seems preferable to phenytoin or phenobarbitone as the first choice for the treatment of appropriate types of epilepsy in young girls and women in their reproductive years'.*[38]
Nov 1981	Published article	Drug and Therapeutics Bulletin[39] stated under the following regarding teratogenicity of sodium valproate: '*30 pregnancies in women taking valproate alone are known and 24 of them were successful and resulted in a normal child; three children were abnormal and there were three spontaneous abortions. In the few cases with congenital abnormalities in the fetus a causal relationship to valproate is uncertain*.'
Oct – Dec 1982	Published article, Sanofi written evidence	A preliminary report by Dr Robert of the Rhône-Alpes monitoring system associated valproic acid exposure in utero with spina bifida in October.[40] This data was also shared with Sanofi directly, who shared a copy with the DHSS. In November, the 'Clearinghouse letter', an update from the September meeting of the International Clearinghouse for Birth Defects Monitoring Systems[41] described the data presented by Dr Robert at the meeting, and states: '*We believe women who have been exposed to valproic acid in the first trimester should be informed of the risk [of spina bifida] and offered prenatal counselling*.' (p1096)

[38] Teratogenic risks of antiepileptic drugs. BMJ, 1981; 283: 515-516.
[39] Sodium valproate reassessed. Drug and Therapeutics Bulletin 1981;19:93-95
[40] Robert and Guibaud (1982) Maternal valproic Acid and Congenital Neural Tube Defects. Lancet 8304: 937 Further papers expanding on these findings were published in 1984 (The Lancet, December 15) and 1986 (European Neurology, 25:436–443) using a Lyon dataset, which the authors argue strongly support the association between valproate and spina bifida.
[41] Bjerkedal, T et al. Valproic acid and spina bifida. Lancet, 1982; ii:1096

		This was followed by a column in the Lancet the next month[42] which summarised the evidence available to date, including reports to the manufacturers. It called for urgent action to confirm the association using data from registries. It reiterated the guidance from the datasheet and urged that decisions on therapy must rest on clinical judgement. In response to the Clearinghouse Letter, the Lancet suggested that since the risks reported relate to spina bifida, women could be offered amniocentesis.
Oct 1982	USA	These studies were highlighted by the CDC in October,[43] and updates published in August the following year.[44] In 1982 Abbott also issued a 'Dear Doctor' letter drawing attention to these studies and updates to the datasheet for Depakene.[45] The letter also reminds doctors that '*All anticonvulsants carry a warning of potential human teratogenicity in their labelling. Some of these drugs, i.e., phenytoin, trimethadione, paramethadione and valproic acid, have now been associated with increased risk of specific congenital defects*'.
Dec 1982	Published article	*Jeavons*[46] - Review of thirteen published reports and further unpublished cases (including reports received by Labaz), totalling 196 pregnancies of known outcome. Of these, 39 babies had congenital abnormalities, including 9 with neural tube defects. Jeavons noted that that normal outcomes are less likely to be reported, and repeated his previous request that the outcome of all pregnancies be reported to the manufacturer for improved monitoring. This was published alongside two other letters responding to the data published by Bjerkedal.[47] MacRae also draws attention to the possibility of bias in studies of this design.
Dec 1982	Sanofi/ MHRA written evidence	Sanofi state that DHSS indicated they did not believe the data available at that time were sufficient to establish a causal connection between use of sodium valproate and neural tube defects or that any change to the data sheet for Epilim was necessary, save for the inclusion of advice to doctors that pregnancies in women prescribed sodium valproate should be carefully monitored.

[42] Valproate and Malformations. The Lancet. December 11 1982. 8311: 1313
[43] CDC. Morbidity and Mortality Weekly Report. Valproic Acid and Spina Bifida: A Preliminary Report – France. October 29, 1982 / Vol. 31 / No. 42.
[44] CDC. Morbidity and Mortality Weekly Report. Valproate: A New Cause of Birth Defects – Report from Italy and Follow-UP from France. August 26, 1983 / Vol. 32 / No. 33.
[45] A copy of this can be found in the evidence from Leigh Day (on behalf of FACSaware, OACS, OACS Ireland, Valproate Victims) – In file: *'Evidence submitted to the Review following its Oral Hearings - october update*'
[46] Jeavons, PM. Sodium valproate and neural tube defects. The Lancet. December 4 1982. 1282-1283
[47] Stanley, OH and Chambers; Macrae, KD. Sodium valproate and neural tube defects. The Lancet. December 4 1982. 1282-1283

		On the 16th December the CSM[48] considered two papers on the teratogenicity of sodium valproate, which included: reports on teratogenicity from France; articles in the professional and non-professional press; and data received from the Company (the manufacturer). They agreed with the licensing authority that no formal action was required against the product licences, but would not object to an amendment proposed by the Company that '*pregnancy should be carefully monitored in women receiving Epilim*'. The Committee agreed that an item should be included in Current Problems as soon as possible. At this meeting the Committee noted a study on maternal drug histories and congenital malformations was run by the CSM with the OPCS, and that there was a need for specific research into the role of anticonvulsant therapy in antiepileptic mothers in increasing the risks of congenital malformations of the foetus.
Jan 1983	Sanofi	Following discussions with the DHSS, the datasheets for Epilim formulations were amended to add advice to prescribers that the use of sodium valproate, like certain other anti-convulsants, '*should be carefully monitored*' during pregnancy.
January 1983	Published article	*Bailey et al.*[49] – Report two cases of physical malformations in children born to women on valproate during the pregnancy. They refer to data received from Labaz: '*33 pregnancies in which valproic acid was the sole anticonvulsant.. resulted in 25 normal babies, four spontaneous abortions, and four infants with congenital malformations (two with meningomyelocoeles, one with syndactyly, and one with a small ventricular septral defect).'* The authors note: '*Valproic acid and carbamazepine have been recommended in preference to phenytoin and phenobarbitone as anticonvulsants for women of childbearing age.. [these cases] may call into question the wisdom of this advice with respect to valproic acid.*'

[48] MHRA written evidence. CSM Minutes of the meeting held on Thursday 16 December 1982
[49] Bailey, CJ et al. Valproic acid and fetal abnormality. Br Med J (Clin Res Ed) 1983: **286**(6360): 190

January 1983	CSM	The CSM's "Current Problems"[50] publication featured an article '*Sodium Valproate (Epilim) and Congenital Abnormalities*'. The article notes the increased incidence of congenital malformations in children exposed to AEDs in utero, and recent data regarding neural tube defects. It discusses the difficulty in interpreting results, including determining the extent to which the medication or the disease has an effect. It advises that treatment should not be withdrawn due to the risk of foetal hypoxia due to maternal seizures. It concludes that there is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other.
Feb 1983	Hansard [51]	[03 Feb] Written question about when DHSS first received reports on valproate risk during pregnancy, assessment of Lancet report, and any steps taken. The response did not answer the first question, and gave an overview of the warnings about teratology in animals. It stated that the CSM has considered reports (including in the Lancet) and concluded there was no clear evidence that this drug was safer or more dangerous in this respect than other similar drugs used in the treatment of epilepsy. The response finally pointed to the advice to doctors in 'Current Problems No. 9' [Jan]. This question was also raised again on the 18th April, as well as a call for a public inquiry into the use of valproic acid. The response [28 April] referred to this earlier answer, and to the CSM 'Current Problems' publication. Additionally, it drew attention to similar action taken by the FDA in the US. It should also be noted that concerns around this time were also around other side effects (not related to use during pregnancy).
Apr 1983	Sanofi written evidence	International symposium of epilepsy and sodium valproate held, supported by Sanofi. The report[52] presented the papers given at the symposium. Sanofi provided a summary of one paper, 'Teratogenicity of Anti-epileptic Drugs' (Meinardi and Lindhout) which expressed concerns about the risk of congenital malformations in children exposed to phenytoin during pregnancy, and referred to debate among specialists about determining the effect of AEDs and maternal epilepsy itself. The paper concluded that the safety of AEDs during pregnancy was uncertain, and that further large-scale research is required.

[50] Committee on Safety of medicines. Current Problems. 1983. Number 9. *Sodium Valproate (Epilim) and congenital abnormalities*

[51] Hansard. 03 February 1983. Volume 36 Column 182. Epilim. http://bit.ly/2X1Jq8G; 18 April 1983. Volume 41. Epilim. http://bit.ly/2zL3VJt; 28 April 1983. Volume 41. http://bit.ly/2VYJx4c

[52] Third International Symposium on Sodium Valproate: proceedings of a symposium held at the Beau Sejour Conference Centre, St. Peter Port, Guernsey, Channel Islands, April 1983; Ed P.M. Jeavons; British Journal of Clinical Practice 1983; Symposium supplement 27

Sept 1983	BNF No. 6	Section on 'Prescribing in Pregnancy' updated to include: '*Sodium valproate – risk in 1st trimester – May possibly be teratogenic*'
1984	Epilepsy Action	British Epilepsy Association (now Epilepsy Action) magazine *Epilepsy Now* ran an article about women with epilepsy, highlighting that '*pre-conception counselling is an important part of the medical management of women with epilepsy*.'
Feb 1984		Bulletin issued by the WHO[53] included a section on 'Valproate and Pregnancy' which considered the Rhône-Alps data. The bulletin concluded that this data did not identify valproate as a more potent teratogen than other AEDs, and noted that regulatory authorities had not further restricted use (beyond the warnings already included in the datasheets).
Sept 1984	BNF No. 8	Section on 'Prescribing in Pregnancy' updated to include: 'Sodium valproate – Risk in 1st trimester – Increased risk of neural tube defects reported but not substantiated'
Nov 1984	Published articles	*DiLiberti et al.* [54] – case reports (seven children) describing 'Foetal Valproate Syndrome'. All had characteristic facial appearance, four had other congenital abnormalities, and two had psychomotor delay. A subsequent letter to the journal[55] noted the confounding effect of polytherapy, and other factors.
Nov 1984	Published articles	*Kelly*[56] - This paper reviewed literature on the teratogenicity of all anticonvulsant drugs, including case-control studies, studies on specific anticonvulsants, prospective studies, and animal studies. As part of the concluding comments, Kelly notes: • The infants of epileptic mothers on anticonvulsant treatment during pregnancy have a rate of major malformations which is two to three times that of the general population. • While the data are limited to France, the evidence suggests a 1% risk of spina bifida to infants exposed in utero to sodium valproate during the first trimester.

[53] A bulletin issued by the World Health Organisation ("WHO"), "Drug Information January - December 1983", included a section entitled "Valproate and Pregnancy" – *from written evidence provided by Sanofi*
[54] DiLiberti, JH et al. The Foetal Valproate Syndrome. Am J Med Genet 1984; 19(3) 473
[55] Chessa, L and Ianetti, P. Fetal valproate syndrome. Am J Med Genet 1986; 24(2): 381-382
[56] Kelly, TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. American Journal of Medical Genetics 1984: **19**(3): 413-434. This is 1 of a 4 part paper, including: Teratogenicity of anticonvulsant drugs II: A prospective study; III: Radiographic hand analysis of children exposed in utero to diphenylhydantoin; and IV: The association of clefting and epilepsy

		• There are inadequate data at the present time to assign significant teratogenicity to any anticonvulsant drug other than trimethadione, paramethadione, and diphenylhydantoin, and possibly, valproate. Kelly describes the methodological issues in all studies of clinical teratology in humans. He calls for further *'multicenter, collaborative protocols designed prospectively to identify at risk pregnancies and evaluate in detail the newborn status and subsequent growth and development of exposed infants with adequate controls.'*
March 1985	Published articles	*Bertollini et al.*[57] - Case control study using Italian Multicentric Registry of Birth Defects over period 1980-1983. Found overall relative risk of having a malformed baby among pregnant epileptic women was 1.87. Spina bifida, congenital heart defects, cleft lip and palate, and hernia were more frequent than expected among babies with maternal epilepsy. A statistically significant association was observed between spina bifida and valproic acid was observed. No other anticonvulsant tested showed any association with any type of malformation.
1986	Published article	*Robert et al* [58]- Survey of women with epilepsy totalling 148 pregnancies, compared with control of computerised population registry. 17.7% of the infants born to women with epilepsy had major malformations, and no major malformations were observed in the 'no drug' group.
March 1986	BNF	BNF (No. 11) advised: *'4.8 Antiepileptics* *Pregnancy. During pregnancy, plasma concentrations of antiepileptics should be frequently monitored as they may fall, particularly in the later stages. There is an increased risk of teratogenicity associated with the use of anticonvulsant drugs, but this is in practice slight and, generally speaking, prescribing in pregnancy should follow the same principles as that in non-pregnant patients. Breast-feeding is acceptable with all the antiepileptic drugs, taken in normal doses, with the possible exception of the barbiturates.'*

[57] Bertollini, R et al. Maternal epilepsy and birth defects: a case-control study in the Italian Multicentric Registry of Birth Defects (IPIMC). Eur J Epidemiol 1985: 1(1): 67-72.
[58] Robert et al. Evaluation of Drug Therapy and Teratogenic Risk in a Rhone-Alpes District Population of Pregnant Epileptic Women. Eur Neurol 1986;25:436–443 https://doi.org/10.1159/000116048

May 1986	Published article	*Lindhout and Schmidt*[59] - Collated data from 13 ongoing prospective studies on prevalence of spina bifida and/or anencephaly among infants with first trimester exposure to valproate/other antiepileptic drugs/mothers with epilepsy unmedicated/fathers with epilepsy/healthy controls. Results confirmed valproate exposure is associated with increased risk of neural tube defects.
Sep 1986	Sanofi written evidence	Following the conclusions of the 1985 CRM Annual Report (later published in the BMJ), the Epilim data sheets were changed, to expand the existing information on use during pregnancy to reflect the data on animal teratogenicity and to include an entry summarising the potential risks in humans.
Dec 1986	Published in BMJ	The Committee on Safety of Medicines and the Committee on Review of Medicines recommended that warnings should be included in data sheets to enable a doctor to make a balanced assessment between risks to fetus and benefits to mother.[60] This should include information on animal data, human population studies and anecdotal reports, and guidance on interpretation. Specimen warnings were also provided.
1987	Epilepsy Action	British Epilepsy Association's '*The Medical Management of Epilepsy*' information booklet outlined the need for women with epilepsy to consult a doctor before becoming pregnant.
Aug 1987	Sanofi written evidence	Sanofi submitted data to the CRM to support the review of the Product Licences for Epilim Plain Tablets and Epilim Syrup, as requested by the DHSS.
Sept 1987	BNF 14	Update to section on sodium valproate. Cautions for sodium valproate now include *'pregnancy and breast-feeding'*
Nov 1987	Published article, Sanofi written evidence	*Winter et al.* [61] – Case reports of four children (1 pair of sibs), describing common facial appearance and other abnormalities (hypospadias, cleft palate, and digital anomalies). They report that two of the four cases showed signs of developmental delay, but that a prospective study would be needed to assess the actual risks. All cases had been reported to the regulatory authority by clinicians or Sanofi.

[59] Lindhout and Schmidt. In-utero exposure to valproate and neural tube defects. Lancet 1986; 14 June: 1392
[60] CSM/CRM Update - Pregnancy warnings in data sheets. BMJ 1986; 293, 1495
[61] Winter et al. Foetal Valproate Syndrome: Is there a recognisable phenotype? J Med Genet 1987; 24: 692

Jan 1988	Published article	*Ardinger et al* [62] - Collection of case reports in which they looked for manifestations of Fetal Valproate Syndrome as described by DiLiberti et al (1984). 17 infants were considered, and the authors describe their findings overall in agreement with DiLiberti et al. Features included: growth deficiency and microcephaly when exposed to valproate in polytherapy; neurodevelopmental effects, and craniofacial anomalies. Features also found following exposure to other anticonvulsants included urogenital anomalies, digital anomalies, and heart defects.
March 1988	Sanofi written evidence	ABPI issued guideline: 'Patient Information; Advice on the Drafting of Leaflets' recommending provision of PILs to supplement advice given by doctors and pharmacists.[63]
March 1988	BNF 15	'Prescribing in pregnancy' information updated to include: 'Antiepileptics. Benefits of treatment outweighs risk to the fetus;...'
June – Aug 1988	Sanofi written evidence	Sanofi applied to the DHSS in June to update the pregnancy warnings on all formulations of Epilim. DHSS refused, but then requested these changes in August for the formulations considered by the CRM. Sanofi responded, requesting approval for changes to all formulations.
Sep 1988	BNF 16	Updated following statements on valproate: Chapter: Prescribing in pregnancy *'Valproate: Increased risk of neural tube defects reported; neonatal bleeding and hepatotoxicity also reported.'*
Oct 1988	Sanofi written evidence	Sanofi received a letter from Dr Keen of the Association for Spina Bifida and Hydrocephalus, which expressed concern at the reported association between use of sodium valproate in pregnancy and spina bifida in exposed infants and suggested that the data sheet for Epilim could be modified to provide a clearer warning. Considering this alongside other emerging data, Sanofi commenced their application to vary the product licences for oral Epilim, and proposed revised data sheet wording with specific reference to spina bifida and neural tube defects. It also instructed doctors that patients should be informed of the possible risks associated with use of the valproate during pregnancy.

[62] Ardinger et al. Verification of the fetal valproate syndrome phenotype. American Journal of Medical Genetics 29(1): 175-185

[63] See also this announcement from the ABPI: Wells, F. O. Patient Information - the Present and the Future. Journal of the Royal Society of Medicine 1990 **83**(5): 300-302.

Dec 1988	Published article	*Lancet* [64] – Systematic review estimated a higher relative risk of spina bifida in children exposed to valproate in utero compared to those whose mothers have untreated epilepsy or epilepsy treated with other AEDs. However it goes on to say that there is a lack of 'high quality evidence', and that the main results to date have appeared in letters in correspondence columns and limited circulation registry reports. It concluded that while congenital malformation registries have been successful in identifying new teratogens, they have failed to present the data in a way that leads to optimum practical action.
1989		An MRC Working Party on Clinical Research into Epilepsy was established. This identified '*pregnancy and "foetal factors"*' as one of several areas of priority for clinical research.[65] A paper presented by Dr David Chadwick highlighted the '*particular need for large-scale epidemiologically-based research into the incidence of foetal abnormalities in babies born to women with epilepsy, to determine the risk incurred from treatment with anti-epileptic drugs. The relationship of these abnormalities to the occurrence of seizures during pregnancy or genetic links between epilepsy and foetal abnormalities also requires assessment.'* [66] Dr Chadwick went on to publish a number of papers on the teratogenicity of antiepileptic drugs (see multiple entries below).
Jan 1989	Sanofi written evidence	Sanofi submitted applications for variations to the product licences for Epilim, and agreed with DHSS that these should include estimated risk of neural tube defects, recognising the limited available evidence.
Apr 1989	Sanofi written evidence	The applications to amend the data sheets for Epilim were approved by the regulatory authority to incorporate the following wording: *'Women of child-bearing age.* *An increased incidence of congenital abnormalities in off-spring born to mothers with epilepsy both untreated and treated has been demonstrated.* *There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.*

[64] Anonymous. Valproate spina bifida and birth defect registries. Lancet 1988; 2: 1404.
[65] FD 23/3403 Working party on clinical research into epilepsy
[66] Minutes of the first meeting of the MRC Working Party on Clinical Research into Epilepsy. 1 Sept 1989

		In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and the patients should be informed of these and the need for screening.' At the request of the regulatory authority, Sanofi sent copies of the revised data sheet to all GPs and relevant hospital doctors, with a covering letter which said '*The datasheet has always drawn attention to the use of Epilim in women of child bearing age and the need for monitoring. This has now been extended to provide more specific and practical advice based on appropriate ante-natal screening and informed counselling.'*
Apr 1989	Sanofi written evidence	Sanofi supported an international symposium intended to promote debate on the benefits and risks of epilepsy treatments. Papers given by exports in epilepsy were published by the Royal Society of Medicine.[67] During a session, 'Management of the Pregnant Patient with Epilepsy', an obstetrician, Dr Robertson, emphasised the potential risk to the foetus as a result of seizures in the pregnant mother; and a neurologist, Professor Loiseau, commented on the risk of major malformations, minor anomalies and developmental disturbances in children born to mothers with epilepsy, stating that the risk of such matters was multifactorial *'with genetic, environmental and therapeutic components'*. Professor Loiseau also raised the issue that all epileptic drugs are weak teratogenic agents, and that women may be reluctant to change their medication if they find it beneficial, and that all such pregnancies should be monitored.
May 1989	Published article	*Oakeshott and Hunt*[68] – Three case reports of spina bifida in children born to women taking sodium valproate in the period 1983-1986, who were unaware of the risk and were not offered prenatal diagnosis.
Aug 1989	Sanofi written evidence	The PILs for the various Epilim formulations were approved by DHSS. In line with the guidance from the ABPI, in addition to the general advice for patients to consult their doctor or pharmacist for further information, these contained three statements relating to pregnancy: Large bordered box under the heading "*Things to remember about Epilim*", advised patients: '*If you are likely to become pregnant, tell your doctor.'*

[67] Fourth International Symposium on sodium valproate and epilepsy: proceedings of a symposium held in St Helier, Jersey, Channel Islands, April 1989; Ed D Chadwick; Royal Society of Medicine; International Congress and Symposium Series 152

[68] Oakeshott P and Hunt GM. Lesson of the Week: Valproate and spina bifida. BMJ 1989; 298: 1300

		"Before taking your medicine" section, which set out a number of questions under the following sentence: '*If you can answer YES to any of the following questions tell your doctor. He may need to give you special instructions*.' The question aimed at women of child-bearing age stated: '*Are you pregnant or likely to become pregnant?*' Towards the end of the PIL: '*Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.'*
Nov 1989	Published article	*Chadwick*[69] - In a response to the editorial, Chadwick discussed the balance of benefit of risk and benefit of treatment with various anti-epileptic drugs, including sodium valproate and carbamazepine, for women of childbearing age, including the risks of withdrawal. He concluded that those for whom valproate is most effective require '*specific counselling of the small risks of valproate to any pregnancy and needing screening of any pregnancy for neural tube defects within the first trimester. Patients themselves can probably best decide whether they wish to take the most effective drug and accept a small risk of neural tube defect or to take a less optimal drug that might be somewhat safer in pregnancy.'*
1990		In this year, lamotrigine and oxcarbazepine were licensed for use in the UK.
1990	Published article	*Hunter and Allen*[70] - Prospective control study of pregnancies in 88 epileptic women. The authors found a higher incidence of talipes (commonly known as 'club foot') in this group compared to the incidence in the local population. In total there were eight minor and one major congenital malformation amongst the 92 babies, within the range of population estimates available to them. In addition they did not find that seizures during pregnancy were associated with malformations. They note that 73% of the cohort were managed on a single anticonvulsant drug, which may have accounted for the good results in this population.
1990	Published article	*Yerby and Leppik* [71] - Review found that no anticonvulsant drug can be considered absolutely safe in pregnancy, and women should be informed of the risks. They found valproic acid to be the only anticonvulsant with a specific pattern of major malformations – a risk of spina bifida of 1-1.5% (20 times that of the general population).

[69] Chadwick D.. Epilepsy in women of childbearing age. British Medical Journal 1989; 299 :1163 doi:10.1136/bmj.299.6708.1163-b

[70] Hunter R and Allen E, The course and outcome of pregnancy in women with epilepsy - a 6-year prospective study, J.Obstet.Gynaecol., 1990, 10(6), 483-491

[71] Yerby, MS & Leppik, I. Epilepsy and the outcomes of pregnancy. Journal of Epilepsy 1990: 3(4): 193-199 doi: 10.1016/0896-6974(90)90046-2

Sep 1990	Sanofi written evidence	The CRM granted a renewed licence for Epilim Plain Tablets.
1991	Published document	*Chadwick et al* [72] – highlighted the teratogenic risks of sodium valproate and that women should be made aware of this.
1991	Sanofi written evidence	Sanofi set up a computerized database for recording suspected adverse drug reactions in this year (prior to this, suspected adverse drug reactions were collected by Sanofi using a non-computerised system.)
Jan 1991	Sanofi written evidence	The CRM granted a renewed licence for Epilim Syrup.
May 1991	Published guidelines	Chamberlain [73] - As part of a guide on care of pregnant women with chronic medical conditions, Professor Chamberlain offered the following advice regarding epilepsy: • GP should consult a neurologist about each individual patient before making recommendations • Most antiepileptic drugs have some extent of teratogenic risk • Epileptic women have an increased risk of having babies with malformations even without treatment. • There is a risk to the embryo if the woman has a series of convulsions when anticonvulsant treatment is withdrawn (this therefore must be balanced with the teratogenic risk of antiepileptic drugs) • If a woman has not had a recent fit, her treatment may be stopped or modified for pregnancy • If she needs treatment, the same dose should be continued • Sodium valproate treatment '*seems to be associated with a lower risk of fetal neural tube defects and might be substituted.*' • If seizure frequency changes, blood concentrations of anticonvulsants should be checked • Folate absorption is changed by antiepileptic drugs, therefore prophylactic folic acid should be given during pregnancy, and vitamin K to newborns.

[72] Chadwick, D et al. The management of epilepsy in General Practice. Roby Education. 1991. Referenced in Sanofi written evidence.
[73] Chamberlain, G. ABC of antenatal care. Medical problems in pregnancy. BMJ 1991; 302(6787): 1262

		In subsequent correspondence, Dr Orrell [74] noted his surprise at the suggestion that sodium valproate may be preferred, drawing attention to the increased risk of neural tube defects reported by Lindhout and Schmidt, and to information included in the datasheet which advises that patients should be informed of the risks and that screening should be provided. Orrell also reiterated the need for informed counselling, and consistent advice from all practitioners managing the care of the patient during pregnancy. He also drew attention to the advice of Oakeshott and Hunt. In his reply, Chamberlain[75] stated: '*the teratogenic effects of various therapeutic regimens and their relation with background diseases is still mostly unproved*.' He described a recent review which warned of the teratogenic effects of a number of anticonvulsant drugs (phenytoin, hydantoin, troxidone (trimethadione), primidone, ethosuximide, and carbamazepine and sodium valproate). He noted that monotherapy is preferable, and suggested that '*Dr Orrell is probably right that sodium valproate should not be given to women in early pregnancy because of its teratogenic associations. It may be possible either to reduce the dose in the first trimester or to substitute another anticonvulsant that currently is thought to be less teratogenic.*' In addition, he briefly gave his view on the screening methods available, stating that a detailed ultrasound is preferable.

[74] Orrell, RW. Sodium valproate in pregnancy. BMJ 1991; 303:56 doi: 10.1136/bmj.303.6793.56-c
[75] Chamberlain, G. Sodium valproate in Pregnancy: Author's reply. BMJ 1991;303:57 doi:10.1136/bmj.303.6793.57

Sep – Oct 1991	Sanofi written evidence	Based on regular surveillance, Sanofi applied to make further changes to the Epilim data sheet. Medicines Control Agency (MCA) approved the following wording: *'Women of child-bearing age.* *An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.* *The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.* *In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.'*
Nov 1991	Sanofi written evidence	Product licence for controlled release formulation of Epilim approved. PIL (approved Jan 1992) contained same wording as other oral Epilim formulations.
1992	EC	European Commission issued Directive on labelling of medicinal products for human use, to ensure users have full and comprehensible information so that medicines could be used safely and effectively.[76]
Apr 1992	Published article	*Delgado-Escueta and Janz*[77] - Published consensus guidelines, which assessed the available information regarding AEDs. This advised that: • All women with epilepsy of childbearing age should be advised of the increased risk of malformations if they are treated with AEDs • Children of mothers with epilepsy (with or without treatment) tend to have slightly more minor anomalies than children of fathers with epilepsy or control subjects. • It is currently not known know which of the four major AEDs (phenytoin, carbamazepine, valproate, and pheno-barbital) is the most teratogenic • If treatment is required, the first-choice drug should be used as monotherapy at the lowest effective dose.

[76] European Commission. Council Directive 92/27/EEC on the labelling of medicinal products for human use and on package leaflets. March 1992.
[77] Delgado-Escueta and Janz. Consensus Guidelines: Pre-conception Counselling, Management, and Care of the Pregnant Woman with Epilepsy. Neurology 1992; 42 (Suppl 5): 149

		• Diet prior to conception and during pregnancy should contain adequate amounts of folate. • Prenatal screening should be offered, and patients should be followed closely • More than 90% of women with epilepsy who receive AEDs during pregnancy will deliver normal children free of birth defects.
June 1993	MHRA written evidence	A reminder was published in the MCA's bulletin 'Current Problems in Pharmacovigilance' [78] regarding neural tube defects associated with valproate and carbamazepine including the need for counselling and screening of women.
Sept 1993	BNF 26	In March 1993, information in section '4.8 Antiepileptics' was updated to include more detailed information regarding polytherapy, drug interactions (signposting to oral contraceptive interactions) and withdrawal. In September 1993, the following warning was included under the subheading '*Pregnancy and breastfeeding'*: *'**Important:** in view of the increased risk of neural tube defects associated with carbamazepine and valproate the **CSM** has advised that women taking these drugs who may become pregnant should be **informed of the possible consequences** and those who wish to become pregnant should be referred to an appropriate specialist for advice. Women who become pregnant should be **counselled** and offered **antenatal screening** (alpha-fetoprotein measurement and a second trimester ultrasound scan).'* This information was boxed for emphasis in 1995. In 1996 recommendations were included to supplement with folate to counteract the risk of neural tube defects. In 1997, additional advice was included that the increased risk of teratogenicity associated with AEDs is "reduced if treatment is limited to a single drug".
Dec 1993	Sanofi written evidence	Following an application by Sanofi, the MCA approved the following amendment to the data sheets for Epilim: *'Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.*

[78] CSM/MCA. *Neural tube defects associated with sodium valproate and carbamazepine – need for counselling and screening.* Current Problems in Pharmacovigilance. Vol. 19. June 1993. https://webarchive.nationalarchives.gov.uk/20090218151445/http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2024463

		The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.'
1994	EC	EC Directive on the labelling of medicinal products for human use and on package leaflets implemented into UK legislation.[79]
1994		Gabapentin licensed for use as an antiepileptic drug in the UK.
1994	Sanofi	The product licence for Epilim Liquid was renewed and the format of the PIL revised in accordance with the legislation. The other PILs were updated at the same time to ensure consistency.
March 1994	Hansard [80]	[09 March] Written question on in utero effects of sodium valproate. The response stated that '*articles in the medical literature and spontaneous reports received by the Committee on Safety of Medicines indicate that there is an increased risk of birth defects in children whose mothers take anti-epileptics. In particular, the use of sodium valproate in early pregnancy is associated with neural tube defects. However, the risks to both mother and child of inadequate treatment of epilepsy during pregnancy are also well recognised and need to be balanced against the risk of birth defects. For this reason many women continue taking anti-epileptics during pregnancy.'* It also drew attention to the 1983 and 1993 bulletins in 'Current Problems', and that information can be found in product data sheets and the BNF.
April 1994	Published article	*Christianson et al* [81] – Case reports of two sibling pairs exposed to valproic acid in utero. One of each pair had presented for assessment of developmental delay, and the sibling subsequently examined.

[79] The Medicines (Labelling) Amendment Regulations 1992. SI 1992/3273.
The Medicines (Leaflet) Amendment Regulations 1992. SI 1992/3274.
The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994. SI 1994/3144.
[80] Hansard. 09 March 1994. Volume 239 http://bit.ly/2PHtGFI
[81] Christianson, AL et al. Fetal Valproate Syndrome: Clinical and Neuro-developmental Features in Two Sibling Pairs. Developmental Medicine & Child Neurology 1994; 36: 361-369. doi:10.1111/j.1469-8749.1994.tb11858.x

Aug 1994	Sanofi written evidence	The revised PILs were approved and included the following wording: *'It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take sodium valproate during pregnancy to control their epilepsy have about a 1% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.'*
Aug 1994	Published article	Lindhout and Omtzigt[82] - review outlining management of teratogenic risks of AEDs. Absolute risk of major malformations in infants exposed to AEDs in utero is about 7-10%. Risk factors include: high maternal daily dosage or serum concentrations, low folate levels, polytherapy, and generalized seizures during pregnancy. Adverse pregnancy outcomes including congenital heart malformations, facial clefts, spina bifida aperta, hypospadias, growth retardation, and psychomotor and mental retardation, "*are associated with, although not necessarily caused by, AED exposure*." Some specific defects can be causally related to specific AED exposures. The guidance states that to prevent teratogenic side effects, they advise treatment only when absolutely necessary, with the most effective AED in the lowest possible daily dose, divided into at least 2-3 administrations. High-dose folate supplementation should be given to reduce the risk of neural tube defects. Prenatal diagnosis should be offered (depending on parental attitudes). Finally the authors note that there are many new AEDs available, which will make prospective evaluation of pregnancy outcomes even more important.
Late 1994	Sanofi written evidence	Lecture given by Professor Lindhout at the Walton Centre in Liverpool on epilepsy in pregnancy. This was attended by a representative of Sanofi who prepared a written note, and there is no published version of the lecture. However this does reflect the paper by Lindhout and Omtzigt above.

[82] Lindhout, D and Omtzigt, JG. Teratogenic Effects of Antiepileptic Drugs: Implications for the Management of Epilepsy in Women of Childbearing Age. Epilepsia 1994; 35: S19-S28. doi:10.1111/j.1528-1157.1994.tb05952.x

		The note indicates that Professor Lindhout commented on the difficulties carrying out research in this area (e.g. low frequency, requires large patient sample; genetic factors related to epilepsy type may influence congenital abnormalities; child development may be influenced by a mother with severe epilepsy). The note also states that Professor Lindhout referred to new data which suggested a dose effect between sodium valproate and the incidence of spina bifida, and that peak plasma concentrations appeared to be significant. His view was that if a therapeutic alternative was available, those on high doses should be switched, but that for some patients there would be no alternative to sodium valproate.
1995		Topiramate licensed for use as an antiepileptic drug in the UK.
Sep 1995	Published article	*Clayton-Smith and Donnai* [83] - A review article published by the Journal of Medical Genetics under the heading "Syndrome of the Month" describes 'Fetal valproate syndrome', which included characteristic facial features and congenital malformations (neural tube defects, congenital heart disease, cleft lip and palate, limb defects and others).
24 October 1995	Hansard [84]	Written questions on plans for opening centres of excellence in treating epilepsy, on 'sodium valproate syndrome', and on providing information about epilepsy and its treatment to doctors and the public. Mr John Bowis (Minister for Health), referred to an announcement made in the House on the 17th January, about the opening of the Centre of Epilepsy and launch of Institute of Epileptology, and programme of co-ordinated initiatives on epilepsy. He set out the work done by the Department and the funding provided to other organisations as part of this programme since January. He also stated that as part of this programme, the Department would be seeking to raise awareness of fetal valproate syndrome among general practitioners and primary care teams.
1996	UKEPR website	UK Epilepsy and Pregnancy Register[85] established to collect and publish information on the frequency of major malformations amongst infants whose mothers take one or more AEDs to prevent seizures. This was joined with the Irish Pregnancy Register (est. 2001) in 2007.[86]

[83] Clayton-Smith, J and Donnai D. Fetal Valproate Syndrome. J. Med Genet. 1995; 32:724
[84] Hansard. 24 October 1995. Volume 264. Epilepsy. http://bit.ly/2PHb609
[85] http://www.epilepsyandpregnancy.co.uk/
[86] **http://www.epilepsypregnancyregister.ie/**

May 1996	Sanofi written evidence	Changes made to the Epilim datasheet to expand warnings in relation to use in pregnancy. This included insertion of the words that associated congenital abnormalities were '*particularly of the limbs*' and an amendment of the risk of neural tube defects to '*1 to 2%*'.
Jun 1996	Sanofi written evidence	Changes made to the PILs for Epilim. This amended the second sentence of the pregnancy warning as follows: *'Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida.'*
Oct 1996	Published article – Norway	*King et al* [87] - Retrospective population study. Changes in incidence of spina bifida and orofacial cleft reflect changes in AED use.
1997	USA	The North American AED Pregnancy Registry[88] established with the major objective of obtaining information on the frequency of major malformations among infants whose mothers had taken one or more AEDs.
Sep 1997	Published article	*Samrén et al* [89] - Analysis of 5 prospective studies (totalling 1,222 children exposed to AED during pregnancy, and 158 controls). Authors found an increased risk of major congenital malformations to children exposed to AEDs during pregnancy, and a significant increase for carbamazepine or valproate in monotherapy. A dose effect was also observed for valproate, with children exposed to over 1000mg/day at a significantly increased risk, especially for neural tube defects.
Jun 1997	Sanofi written evidence	Following presentation given by Dr Peter Turnpenny on 'foetal valproate syndrome', Sanofi requested details of the four children described, who apparently displayed facial dysmorphia and social behavioural problems. Following further discussions, Sanofi provided a grant for a forum to discuss the effects of anti-epileptic drugs on the foetus (held in May 1999).
23 Jun 1997	Sanofi written evidence	Periodic Safety Update Report (PSUR) in relation to Epilim formulations, which covered the period February 1992 to January 1997, was submitted to the UK regulatory authority by Sanofi. The report, which included all events reported worldwide, concluded that there was '*no suspicion of increased frequency or severity of already listed reactions over this period*', that '*no new and relevant information about use in pregnancy was identified during the review period*' but stated '*appropriate monitoring with regard to pregnancy during this period is recommended*'.

[87] King, PB et al. Spina bifida and cleft lip among newborns of Norwegian Women. American Journal of Public Health 1996; 86(10):p1454-1457.
[88] http://www.aedpregnancyregistry.org/about-history/
[89] Samrén EB et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia. 1997 Sep; 38(9):981-90

Sep 1997	Sanofi written evidence	Further variation to Epilim data sheets approved by the UK regulatory authority, to include a warning in respect of the risk of haemorrhagic syndrome in new-born infants whose mothers had taken sodium valproate during pregnancy: '*there may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy*'.
June 1998	Hansard [90]	[17 June] Debate on 'Epilepsy' drew attention to shortage of specialist centres or services.
Dec 1998	Hansard [91]	Written questions on the effects of AEDs during pregnancy [02 Dec] and the representations to the Department of Health on the effects of sodium valproate prescribed during pregnancy [15 Dec]. In response, Ms Tessa Jowell (Minister of State) stated that the Department was not currently aware of any representations on this matter. She stated that risks of AED exposure during pregnancy are known and can be found in authorised product information and the BNF, and that women should be informed of the risks, and referred to an appropriate specialist for advice and antenatal screening. The response closed with a reminder that the risks of epileptic control need to be weighed against the risks to the foetus of these treatments.
1999	OACS Charity	OACS set up to provide support and raise awareness for children affected by Fetal Anticonvulsant Syndromes. It became OACS Charity in 2005.
1999	EURAP webpage	European Registry of Antiepileptic drugs and Pregnancy[92] 'EURAP' launched by a consortium of independent research groups in Europe, and later extended worldwide. Prospective observational study of pregnancies with antiepileptic drugs. The aim was to collect data on the risk of antiepileptic drugs during pregnancy and share it in an international registry.
Feb 1999	Published article	*Kaneko et al*[93] - Prospective cohort controlled study. Exposure to AED in utero was associated with an increase in risk of congenital malformations. The results indicated that malformations can be prevented though avoiding polypharmacy, optimising daily dose and avoiding high levels of valproate in women of childbearing age.

[90] Hansard. 17 June 1998. Volume 314, Column 482. Epilepsy. Debate in Commons Chamber. http://bit.ly/2NO8U4c

[91] Hansard. 02 December 1998. Volume 321. Anticonvulsant Drugs http://bit.ly/2PIEsv0; 15 December 1998. Volume 322. Sodium Valproate. http://bit.ly/2MS7Exq

[92] http://eurapinternational.org/about/

[93] Kaneko, S et al. Congenital malformations due to antiepileptic drugs. Epilepsy Res. 1999; 33(2-3):145-58

May 1999	Epilepsy Action	*Crawford and Lee*[94] - Questionnaire survey carried out among female members of British Epilepsy Association (now Epilepsy Action). 34% of women surveyed had not received any advice about pregnancy, and 25% had not discussed pregnancy with anyone. In the group of women who were planning to have children in the subsequent two years, 20% claimed not to have received any information.
May 1999	Hansard [95]	[25 May] Written question on interactions between contraception and AEDs, and the risks of exposure to AEDs in utero. The response covered known information and drew attention to the SmPCs and PILs. It restated the risks of withdrawal from AEDs to the mother and the fetus, and the need to consider the risks and benefits of treatment options.
Sept 1999	Published article	*Koch et al.*[96] – Prospective study (Germany) Found that AED exposure in utero appeared to have long-term neurodevelopmental effects, with strongest effect in the polytherapy group, and with exposure to primidone.
Sept 1999	Sanofi written evidence	Sanofi provided financial support of £15,000 to Professor Chadwick's group in Liverpool for their study investigating additional educational needs in children born to mothers with epilepsy.
2000	MHRA written evidence	Levetiracetam was issued a centralised marketing authorisation by the European Commission in 2000.
Jan 2000	Published article	*Moore et al* [97] - Retrospective clinical study of children recruited through patient support group for FACS, or referred to genetics service in Aberdeen. Common features included speech delay, joint laxity, glue ear, myopia, autistic features and hyperactivity. Further research in Aberdeen is included below (e.g. Dean et al. 2002, and Rasalam et al. 2005).

[94] Crawford, P & Lee, P 'Gender difference in management of epilepsy—what women are hearing' Seizure 1999; 8: 135–139
[95] Hansard. 25 May 1999. Volume 601. Anti-Epileptic Drugs In Pregnancy. http://bit.ly/2zSYurG
[96] Koch S et al. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 1999; 40(9): 1237-1243
[97] Moore, S et al. A clinical study of 57 children with fetal anticonvulsant syndromes. Journal of Medical Genetics 2000;37:p489-497

Jan 2000	Sanofi written evidence	Correspondence between the MCA and Sanofi regarding a potential drug safety signal of increase risk of developmental delay in children exposed to valproate in utero compared to other AEDs. The MCA was prompted to act by receipt of a draft paper by Professor Chadwick 'Additional Educational Needs in Children Born to Mothers with Epilepsy' (a retrospective postal questionnaire). The paper found an association between additional educational needs and AED exposure, with a higher odds ratio in children exposed to sodium valproate[98].
Feb 2000	Sanofi written evidence	Sanofi report that they corresponded with Professor Chadwick regarding two unpublished papers (a meta-analysis and a retrospective study), and that Professor Chadwick had requested the MCA's statistician to review the data for the retrospective study. The statistician raised some queries;[99] and Sanofi agreed to support a prospective study proposed by Dr Chadwick on neurodevelopmental effects of antiepileptic drugs to address some of these issues. Professor Chadwick's retrospective study was published in January 2001.[100]
Feb 2000	Published article	*Wide et al.*[101] – Prospective control study of 100 children whose mothers were treated with AEDs during pregnancy, and 100 matched controls. Exposed children had a significant increase in the number of minor anomalies, and facial anomalies after carbamazepine exposure. At assessment at 9 months, no effect on psychomotor development was found.
Feb 2000	Hansard [102]	[28 Feb] Debate on 'Epilepsy' regarding the level of healthcare available for people with epilepsy. During this debate particular attention was drawn to the unique needs of women and girls during their lifetime, regarding contraception, fertility, pregnancy and the menopause.
10 Mar 2000	Hansard [103]	Written question on Department's assessment of the side effects of Epilim prescribed to children, and on the use of Epilim during pregnancy.

[98] An odds ratio gives a measure of how likely it is that two factors are connected. If they are independent of each other the odds ratio is one. An odds ratio of over one shows a positive association, a higher value shows a stronger association.
[99] See Sanofi written evidence to the Review – Timeline entries 18 Jan – 3 Apr 2000 for further detail.
[100] Adab, N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy: J Neurol Neurosurg Psychiatry 2001;70:15-21
[101] Wide, K et al. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. Dev Med Child Neurol 2000; 42(2):87-92
[102] Hansard. 28 February 2000. Volume 610. Epilepsy. Debate in Lords Chamber. http://bit.ly/2PEkgub
[103] Hansard. 10 March 2000. Column 863W. Epilim

		Ms. Gisela Stuart (Under-Secretary for Health) responded with answers related to side effects in children. In relation to Epilim exposure in utero, in the UK 22 cases of birth defects for women exposed to the drug Epilim during pregnancy were reported to the MCA/CSM in the period January 1995 – March 2000. She repeated the product information advice about the use of Epilim in pregnancy, contraindications, dosage, and points to the Summary Product Characteristics for full guidance.
Apr 2000	Published article	*Dean et al* [104] - Developed a diagnostic criteria to assist in identifying children who may have fetal anticonvulsant syndrome. 1. History of in-utero antiepileptic drug exposure 2. Presence of characteristic facial appearance 3. Presence of at least one of the following: a. evidence of neonatal withdrawal b. compatible malformation c. compatible childhood medical problem d. compatible developmental history e. compatible behavioural problem 4. Normal relevant investigations for alternative aetiologies (e.g. karyotype, Fragile X mutation analysis, CATCH22 deletion studies)
Apr – Jul 2000	Sanofi written evidence	<u>Ongoing between Sanofi and MCA</u> Sanofi submitted a detailed response to the MCA's concerns about developmental delay in children exposed to valproate in utero. This was based on external expert analysis of Professor Chadwick's study, clinical and preclinical data, reports from the Corporate safety database, and unpublished data. It also reviewed other possible causes of development delay including maternal epilepsy, seizures during pregnancy, genetic and environmental factors. The report concluded that a key issue is the balance of benefits of seizure control against the risk of the AED to the mother and foetus, and that while some studies have shown exposed children have lower scores on cognitive development measures, the evidence to do date does not suggest any one AED has a higher risk than any other of causing developmental delay. Sanofi also pointed out that the use of sodium valproate in women of childbearing age was already restricted as per the SmPC. The MCA requested, and Sanofi provided, details of preclinical studies relating to teratogenicity in rats.

[104] Dean, JCS, Moore, SJ, Turnpenny, PD (2000) Developing diagnostic criteria for the fetal anticonvulsant syndromes. Seizure 9(3):233-234 doi: 10.1053/seiz.2000.0392

		Sanofi submitted the PSUR for sodium valproate for the period 1 February 1997 - 31 December 1999. This included a cumulative review of psychomotor development impairment, and noted that developmental delay had been identified as a new area of interest, and while no definite relationship had been established, this would remain under surveillance.
Aug 2000	Sanofi written evidence	Sanofi, and other pharmaceutical companies, provided financial support for Professor Chadwick's prospective randomised clinical trial 'Standard And New Antiepileptic Drugs' ('SANAD'), which had been underway for a year. Patients were randomised to sodium valproate and other antiepileptic drugs. The primary objective was to study whether there were differences in IQ between mothers and children exposed to AEDs in pregnancy.
Sep 2000	Sanofi written evidence	The data on developmental delay was reviewed by the Pharmacovigilance Sub-committee of the CSM.
Sep 2000	Sanofi written evidence	Sanofi wrote to the MCA confirming that it was sponsoring two studies investigating developmental delay being carried out by Professor Chadwick's group. It also indicated that Sanofi was providing support for two pregnancy registers, the European Registry of Antiepileptic drugs and Pregnancy ('EURAP') and the UK Epilepsy and Pregnancy Register.
Sep 2000	Published article	*Fairgrieve et al* [105] - Prospective study in the North East region showed that women are supervised by their general practitioner, not a neurologist, guidelines are not being followed, and methods of preconception counselling are ineffective.
Dec 2000	Sanofi written evidence	Sanofi proposed changes to the SmPCs in line with company core safety information, other side effects, and with EU guidance regarding wording of existing pregnancy warnings. A new special warning was included concerning the use of Epilim in women of child-bearing age: *'Pregnancy: It is recommended that Epilim be used in women of child-bearing age only in severe cases or those resistant to other treatment because of the potential teratogenic risk to the foetus exposed to valproate in utero. Women of child-bearing age should be informed of the potential risks and benefits of continuing anti-epileptic treatment throughout pregnancy (see also Section 4.6 Pregnancy and Lactation).'*

[105] Fairgrieve, SD et al. Population based, prospective study of the care of women with epilepsy in pregnancy. BMJ 2000;321:674–5

2001	Department of Health	In 2001, the annual report of the Chief Medical Officer stated that epilepsy had '*remained in the shadows for decades.*' It pointed to five earlier reports[106] which remained largely unimplemented, persistence of negative attitudes to epilepsy, and a poorer understanding and commitment to addressing the illness by health services and professionals than for other diseases.[107]
Jan 2001	Published article	*Adab et al.* [108] – Retrospective survey of children exposed to antiepileptic monotherapy and polytherapy in utero. The study found an association between AED exposed school-age children and additional educational needs. The odds ratio of additional educational needs for all AED exposed school-age children compared to unexposed was 1.49, and for valproate monotherapy was 3.40[109]. The authors conclude: '*Although the findings should be treated with caution, they suggest that monotherapy or polytherapy with valproate during pregnancy carries particular risks for the development of children exposed in utero.'* Additionally the authors call for further urgent investigation to clarify and optimise treatment for women with epilepsy who are of childbearing age.
Jan 2001	Sanofi written evidence	The MCA confirmed that the developmental delay data had been discussed extensively at the Pharmacovigilance and Paediatric Sub-Committees of the CSM, who considered that a causal association between developmental delay in infants and exposure to sodium valproate in utero had not been established and that no immediate regulatory action was therefore required.

[106] Including the 1956 Cohen Committee; 1969 Reid Report; Bennet investigation into the Reid Report (J D Morgan and A E Bennet, unpublished reports); 1986 Report of the working group on services for people with epilepsy (Department of Health and Social Security)
[107] Department of Health. On the State of the Public Health: The Annual Report of the Chief Medical Officer of the Department of Health 2001 available here.
[108] Adab N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy: J Neurol Neurosurg Psychiatry 2001;70:15-21
[109] An odds ratio gives a measure of how likely it is that two factors are connected. If they are independent of each other the odds ratio is one. An odds ratio value over one shows a positive association, a higher value shows a stronger association.

Jan 2001	Published article	*Kozma* [110] - A case report of two siblings showing characteristics of FVS. The paper also reviewed the literature from 1978-2000, identifying 69 cases. In this population sodium valproate exposure in utero was associated with a characteristic facial phenotype, and increased risk of musculoskeletal, skin, cardiovascular, genital and pulmonary abnormalities. Other abnormalities included brain, eye, kidney, and hearing defects. Neurodevelopmental effects were seen in 29% of the surviving infants.
Mar 2001	Sanofi written evidence	MCA wrote to Sanofi confirming the CSM's conclusion that: '*…based on the presently available evidence, a causal association had not been established [between sodium valproate and developmental delay'*. However, the authorities considered that treating physicians should have emphasised to them the existing restriction on the use of sodium valproate in women of childbearing age to those who were resistant to other treatments and those who suffered from severe epilepsy. The MCA confirmed that the December 2000 applications to amend the SmPCs for Epilim products addressed these concerns.
Jun 2001	Sanofi written evidence	Sanofi wrote to the MCA submitting the PSUR for sodium valproate for the period 1 January 2000 - 31 January 2001. This PSUR included a cumulative review on "psychomotor development impaired", which concluded that based on data collected on spontaneous reporting: '*no conclusions concerning a causal relationship between valproate and occurrence of "developmental delay" in children born to mothers exposed to valproate in utero can be drawn. This topic will remain under close surveillance by the company*.'
Oct 2001	Sanofi written evidence	The SmPC changes proposed by Sanofi in December 2000 were approved by the MCA.
Dec 2001	Sanofi written evidence	The PSUR for sodium valproate for the period 1 February 2001 to 31 July 2001 did not result in any amendments.
Jan 2002	Sanofi written evidence	Articles raising concerns about the potential teratogenic (congenital malformation) effects of valproate, including some that mentioned the data from the UK Epilepsy and Pregnancy Register, were reported in the general press. These publications related to congenital malformations which were already listed in the SmPC.
Jan 2002	Sanofi written evidence	MCA notified Sanofi that the issue of potential neurodevelopmental delay in children exposed to valproate during pregnancy was being kept under constant review, but for the time being, and pending consideration of data from the UK Epilepsy and Pregnancy Register, no amendment to the warnings and advice contained in the product information for Epilim were required.

[110] Kozma, C. Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. American Journal of Medical Genetics. 98(2): 168-75

Apr 2002	Published article	*Dean et al.*[111] – Retrospective population study (Scotland) of 149 women taking AEDs in pregnancy between 1976 and 2000. Significant differences in developmental delay (speech, motor, global or special educational needs at school) between children exposed to carbamazepine, valproate, phenytoin monotherapy and for those on polytherapy compared to a (smaller) control group of siblings of exposed children who were not exposed to antiepileptic treatment in utero. The paper concludes: *'For a mother considering pregnancy, AED therapy with the drug regimens observed in this study is associated with a two to three fold increased risk of major malformation or developmental delay (relative risk 2.38, 95% CI 1.03-5.51). The developmental disorder is likely to have a multifactorial aetiology, but single drug therapy with valproate, phenytoin, or carbamazepine and polytherapy are all associated with a substantial risk of developmental delay, even when possible genetic factors are excluded… The influence of an impaired mother-child interaction in the early years because of maternal epilepsy or its treatment requires further study. As discontinuation of epilepsy treatment in pregnancy because of the teratogenic risk is not usually an option, the importance of further research into susceptibility factors, the development of safer drugs, and the appropriate counselling and management of epileptic women cannot be overemphasised.'*
May 2002	Sanofi written evidence	Cumulative review on '*psychomotor development impaired*' in the PSUR for sodium valproate did not reach any conclusion, and remained under surveillance by Sanofi.
Jul 2002	Sanofi written evidence	The MCA wrote to Sanofi stating that the CSM had carried out a further review of the safety of sodium valproate in pregnancy, in the context of preliminary data from the UK Epilepsy and Pregnancy Register. The CSM had advised that "there was evidence to suggest that although all antiepileptic drugs were potentially teratogenic, there was an increased risk of teratogenicity with valproate compared with other antiepileptic drugs." In the light of this the CSM had advised the MCA to communicate with prescribers and health professionals about the potential teratogenic risks of sodium valproate and other AEDs.
Aug 2002	Sanofi written evidence	In order to take into consideration recent reports in the scientific literature concerning the potential developmental delay reported in children born to mother with epilepsy, Sanofi modified its company core safety information: *'PREGNANCY*

[111] Dean JC et al. Long-term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet 2002; 39b(4): 251-259

		- Risk associated with epilepsy and antiepileptics *….* *Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.'*
Sep 2002	Sanofi written evidence	Sanofi responded to the MCA's letter of 22 July regarding findings from the UK Epilepsy and Pregnancy Register data. In contrast to the MCA, Sanofi considered the data to reflect the existing scientific literature. They discussed the results with the principal investigator, who agreed the results should be treated with caution in view of potential confounding factors. Sanofi was concerned that the communication to physicians proposed by the MCA could therefore be responsible for unjustified treatment decisions which might jeopardise patients' epilepsy control.
Oct 2002	Sanofi written evidence	Revised wording for the Epilim SmPC was approved by the CSM. Changes proposed included a new Special Warning: *'Women of child bearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic drug of choice in patients with certain types of epilepsy such as generalised epilepsy. In these women who are likely to get pregnant, specialist advice should be sought because of the potential teratogenic risk to the foetus.'* Additionally, the wording regarding congenital abnormalities was updated to include specific reference that the increased incidence of congenital abnormalities related to mothers treated with sodium valproate. At that time, the CSM did not suggest a warning regarding developmental delay should be added.
Oct - Nov 2002	Sanofi written evidence	Sanofi accepted the CSM's proposed wording, and proposed further amendments to reflect the developing scientific literature: *'Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.'*

		Sanofi provided further data as requested by the MCA. This submission reviewed the available literature (including the Dean et al paper) and concluded that children of mothers with epilepsy exposed to AEDs in utero have been shown to have lower scores in cognitive development, and continues: '*Maternal epilepsy and type of epilepsy (generalised versus partial), intra uterine exposure to AEDs, genetic factors, social factors such as parental education and environmental factors may all play a role in increasing the risk of developmental delay in children born to mothers with epilepsy.'*
Nov 2002	MHRA written evidence (MCA)	Working Group on paediatric medicines discussed sodium valproate and developmental delay. This was an update to a paper discussed in November 2000. Minutes of the WG show that they considered that there was now evidence from a number of studies suggesting an increased risk of developmental delay following in-utero exposure. They advised that product information should be updated to include a warning of this risk, that the SmPC wording proposed by the manufacturer was endorsed with some amendments, and that there was a need to communicate this information, without undue delay, for example via an article in 'Current Problems' or via the CSM website.[112]
Dec 2002	Sanofi written evidence	The MCA agreed to Sanofi's request to include in the SmPC for Epilim a warning regarding the possibility of developmental delay in children exposed to valproate during pregnancy. They indicated that the CSM's Paediatric Working Group had concluded that there was now accumulating evidence to suggest a possible risk of developmental delay in infants exposed to anti-epileptics in utero, but there was conflicting evidence implicating valproate and suggested some revision to the wording proposed by Sanofi. *'Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment.'*

[112] MHRA written evidence. Doc 'H. Paediatric Medicines WG Nov 2002. Minutes of the Working Group on Paediatric medicines, meeting held on Wednesday 27 November 2002.

Dec 2002	Published article	*Mawer et al* [113] - Small mainly prospective study showed as association between adverse outcome and dose for sodium valproate, with severe adverse features associated with doses of sodium valproate above 1000mg per day. The authors note that '*Despite its limitations the results of this study add to the growing body of evidence that VPS in pregnancy at doses above 1000mg per day carries a particular risk of adverse outcome. Sodium valproate at such doses should therefore be avoided when pregnancy is likely.*'
2003	Department of Health	An audit of epilepsy services[114] reported that 54% of adults, and 77% of children had inadequate care, with the key problems identified being: lack of timely access to skilled specialists; sparse evidence of structured management plans; triggers for referral were sometimes missed; and professional communication failures. In addition the audit found deficiencies in communication about epilepsy management and hazards between healthcare professionals, patients, their carers and families.
Jan – Apr 2003	Sanofi written evidence	MCA (MHRA from April 2003) proposed the following changes to the Epilim PILs, which were accepted by Sanofi: *'Infants born to mothers who took Epilim during pregnancy may develop less quickly than normal. This may also be because of the mother's epilepsy but the exact cause is not known.'* Sanofi proposed, and MCA/MHRA accepted, specific statement on dose effect in pregnancy: '*The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg per day.*'
May 2003	Sanofi written evidence	Sanofi applied to renew the marketing authorisations for the Epilim product range for a further five years.
Sep 2003	Published article	MHRA – Current problems in Pharmacovigilance article "Sodium valproate and prescribing in pregnancy"[115] which advised medical practitioners of the new data. The key messages included: • *The risk of congenital malformations following in-utero exposure to AEDs is approximately 2 to 3 times higher than in the general population*

[113] Mawer, G et al. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure 2002; 11: 512–518
[114] Department of Health. Improving Services for People with Epilepsy: Department of Health Action Plan in response to the National Clinical Audit of Epilepsy-Related Death. 2003
[115] https://webarchive.nationalarchives.gov.uk/20141206183805/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con007450.pdf

		• *In utero exposure to sodium valproate has been associated with an increased incidence of congenital malformations including facial dysmorphia, and multiple malformations, particularly of the limbs* • *Two retrospective epidemiological studies have also suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Other factors, such as the mother's epilepsy, may also contribute to this risk.* • *Sodium valproate remains the anti-epileptic of choice in patients with certain types of epilepsy* *Following a review of the available data including data from the UK Pregnancy and Epilepsy Register, CSM has advised:* • *Specialist neurological advice prior to starting sodium valproate* • *Pre-conception counselling for women on sodium valproate* • *If taken during pregnancy, sodium valproate should be prescribed as monotherapy, at the lowest effective dose, in divided doses, and as a prolonged release preparation.* • *Folic acid supplementation may reduce risk of neural tube defects*
Oct 2003	Epilepsy Action written evidence	Survey of the members of Epilepsy Action show that women are not receiving information about the possible adverse effects of treatment during pregnancy[116].
Nov 2003	Hansard [117]	One of a number of questions which draw attention to the shortage of specialist epilepsy services, including neurologists [22 Jan], and specialist epilepsy nurses [18 Nov, 09 Dec; and again on 1 May 2007]
Nov 2003	Sanofi written evidence	The MHRA wrote to Sanofi, confirming that it considered the wording of the SmPC to be satisfactory.

[116] Crawford, P & Hudson, S 'Understanding the information needs of women with epilepsy at different lifestages: results of the 'Ideal World' survey' Seizure 2003; 12: 502–507

[117] Hansard. 22 January 2003. Volume 398. National Service Framework for Long-Term Conditions. http://bit.ly/2zR2EAA; 18 November 2003. Epilepsy Nurses. https://publications.parliament.uk/pa/cm200304/cmhansrd/vo031209/debtext/31209-02.htm; 09 December 2003. Volume 415. Epilepsy Nurses. http://bit.ly/2zM5cA1; 01 May 2007. Volume 691. Health: Specialist Nurses. http://bit.ly/2zR8Ok1 http://bit.ly/2zR8Ok1

2003/ 2004	NHS Resolution written evidence; Sanofi written evidence	During the late 1990s, NHS Resolution (then the NHS Litigation Authority) faced a growing group of claims from women and children alleging that exposure to sodium valproate in utero had caused damage. There were 111 claims registered under a group code[118]. In 2003, following their investigation, NHS Resolution obtained advice that claimants had better prospects of success against the manufacturers, Sanofi-Synthelabo. They passed on this advice to the claimants legal representatives and to the Legal Services Commission (now the Legal Aid Agency). In 2004, proceedings were issued against Sanofi. This litigation became known as the Fetal Anti Convulsant or 'FAC Litigation'. The claim was subject to a Group Litigation Order which consolidated the individual claims of more than 100 children across the UK all of whom had been diagnosed with FVS. Group A comprised 100 fully prepared cases; Group B comprised 67 cases issued, served and stayed in order to protect claims which would otherwise become statute barred by the effect of the 10 year long stop.
Mar 2004	Published article	*Fried et al* [119] - Meta-analysis reviewing the occurrence of major malformation rates among children of treated or untreated women with epilepsy and non-exposed controls who do not have epilepsy. The results questioned the commonly held view that epilepsy *per se* represents a teratogenic risk, and the authors suggested that this view may be the result of publication bias. They noted the need for further studies to control for the type, severity and frequency of seizure disorders on teratogenic risk.
Mar 2004	NICE	NICE Technology Appraisal 74 'Newer drugs for epilepsy in adults' published. The guidance stated that the risks of AED exposure in-utero should be discussed with women of childbearing potential, and an assessment made of the risks and benefits. It stated there is insufficient data on the newer AEDs, but advised specific caution in the use of sodium valproate because of the risk to the unborn child (as set out in the Summary of Product Characteristics). It recognised that some women were resistant to other treatments, and should be able to make an informed choice about their treatment. NICE Technology Appraisal 79 'Newer drugs for epilepsy in children' published in April 2004 gave similar advice regarding girls of childbearing potential.

[118] Written evidence provided by NHS Resolution shows the number of claims received by NHS Resolution between 1994 and 2018. Of a total of 118 claims, 6 were settled, with a total of £4,293,264 paid in damages.
[119] Fried S et al. "Malformation rates in children of women with untreated epilepsy. A meta-analysis". Drug Safety March 2004: 27(3): 197-202

May 2004	Sanofi written evidence	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate including all available literature for the period 1 February 2003 – 31 January 2004. The reports of administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the company core safety information (CSI).
May 2004	Sanofi written evidence	The Epilim marketing authorisations were renewed.
July 2004	Published article	*Adab et al.* [120] – Cochrane Review on AEDs in pregnancy considered all studies published between 1966 and December 2003. The authors stated that there was "little evidence about which specific drugs carry more risk than others to the development of children exposed in utero", noted there were few studies on exposure to sodium valproate, and that most studies failed to find a significant outcome in exposure to monotherapy with older AEDs (carbamazepine, phenytoin or phenobarbitone). The authors concluded that: '*Based on the best current available evidence it would seem advisable for women to continue medication during pregnancy using monotherapy at the lowest dose required to achieve seizure control. Polytherapy would seem best avoided where possible. More population based studies adequately powered to examine the effects of in utero exposure to specific monotherapies which are used in everyday practice are required.*'
July 2004	Sanofi written evidence	In light of the paper by Adab and colleagues (published in November 2004), Sanofi made applications to MHRA to include a statement regarding neurodevelopmental risk. The following was subsequently approved for the SmPC (October 2005): '*Some data from studies, of women with epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.*'
Oct 2004	Sanofi	The CSI was updated in October 2004 to reflect the upcoming publication by Adab et al. regarding developmental delay.

[120] Adab N et al., Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev. 2004; (3):CD004848.; online version published 19 July 2004

Oct 2004	NICE	NICE published a Clinical Guideline on 'The diagnosis and management of the epilepsies in adults and children in primary and secondary care' (CG20)[121]. This contained detailed advice on many aspects of the treatment of epilepsy. Appendix B (pharmacological management) confirmed that sodium valproate was a first line drug treatment for all listed seizure types and all but one of the epilepsy syndromes listed. It highlighted the CSM advice published in Current Problems in Pharmacovigilance in 2003 that: '*women of child bearing potential should not be started on sodium valproate without specialist advice*.' The main text of the Guideline emphasised at paragraph 4.11.4A the need for counselling: *'In women of childbearing potential, the risk of the drugs...causing harm to an unborn child should be discussed and an assessment made of the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk to the unborn child.'* It advised information and counselling should be given about '*contraception, conception, pregnancy, caring for children, breastfeeding and menopause*.' It also highlighted that prescribers '*should be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of childbearing potential.*' Appendix D also included a checklist for women, adopted from Epilepsy Action's Women with Epilepsy Checklist which highlighted the need to discuss the teratogenic effect of AEDs.
Oct 2004	Epilepsy Action	Epilepsy Action produced a leaflet for patients *The Epilepsies: You, epilepsy & the NICE Guideline* which highlighted the risk that some AEDs can harm the unborn child.
Nov 2004	Sanofi written evidence	Sanofi submitted an application to the MHRA to vary the marketing authorisations for Epilim products to include a new statement in the SmPC recommending counselling be made available to all women with epilepsy of childbearing potential, and for similar information to be included in the PIL. The MHRA asked Sanofi to also restructure information related to pregnancy in the PIL.

[121] NICE Clinical Guideline: The epilepsies - The diagnosis and management of the epilepsies in adults and children in primary and secondary care 2004 (CG20)

Nov 2004	Published article	*Adab et al.* [122] – Retrospective study of children born to mothers with epilepsy. This follow-up of their 2001 study used structured interviews, clinical examination and psychometric tests alongside hospital records to assess exposure and IQ. The study identified valproate exposure in utero as leading to a risk of developmental delay and cognitive impairment. It also calls for controlled prospective studies of the use of existing and seven new AEDs during pregnancy to identify risk for neurodevelopment effects. Sanofi had sent an early copy of this paper to the MHRA in April.
Nov 2004	Published article	*Vajda et al* [123] – Prospective observational cohort study using the Australian register showed a dose-effect relationship for malformations and exposure to valproate in the first trimester of pregnancy, with high doses of valproate associated with greater risk that lower doses or other AEDs.
Mar 2005	DH	*National Service Framework on long-term conditions* set out 11 quality requirements to improve care, focussing on neurological conditions.[124] NICE and SIGN[125] guidelines published in 2004 - 2005 provide a structure for management of people with epilepsy.
May 2005	Sanofi written evidence	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2004 – 31 January 2005. No new relevant information was identified, and no update was made to the CSI.
Aug 2005	Published article	*Rasalam et al.*[126] – Population based study found that prenatal exposure to AEDs were a risk factor for the development of Autism Spectrum Disorder (ASD), and that sodium valproate appeared to be more commonly associated with ASD than other AEDs.

[122] Adab et al. The longer term outcome of children born to mothers with epilepsy J Neurol Neurosurg Psychiatry 2004; 75: 1575-1583

[123] Vajda, FJ et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. Journal of Clinical Neuroscience 2004 11(8):854-858 doi:10.1016/j.jocn.2004.05.003

[124] Department of Health. The National Service Framework for Long-term Conditions. March 2005.

[125] A copy of the 2005 SIGN guidelines '81: Diagnosis and management of epilepsies in children and young people – A national clinical guideline' can be found here. '*Guideline 70: Diagnosis and management of epilepsy in adults'* was published in 2003. This has now been replaced with '*Guideline 143: Diagnosis and management of epilepsy in adults*' (May 2015, revised 2018).

[126] Rasalam, AD et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005; 47(8): 551-5

Sep 2005	Published articles; Sanofi written evidence	*Morrow et al* [127] - First findings from the UK Epilepsy and Pregnancy Register, using prospective observational information gathered between December 1996 and March 2005, on infants at three months after expected delivery data. The overall rate of major congenital malformations was 4.2% for all AED exposed cases, compared to 3.5% in the offspring of women who had not taken AEDs during pregnancy. The rate was higher for polytherapy than for monotherapy, and for pregnancies exposed only for sodium valproate compared to carbamazepine. Polytherapy containing sodium valproate was associated with a higher risk than those not containing sodium valproate. A trend for dose response for valproate did not reach statistical significance, however infants exposed to more than 1000 mg of valproate had the highest MCM rate for any monotherapy exposure, at 9.1%. *Meador et al* [128]- A preliminary analysis of data from the Neurodevelopmental Effects of Antiepileptic Drugs ("NEAD") study. The data on serious adverse neurodevelopmental outcomes suggested that such outcomes occurred in 10% of carbamazepine, 2% of lamotrigine, 12% of phenytoin, and 24% of sodium valproate exposed children. The NEAD study was ongoing, but the authors considered that the preliminary results raised concerns over the use of sodium valproate as a first-line treatment in women of childbearing potential. The authors stated that they did not consider that the results of this and other studies meant that sodium valproate should never be used in women of child bearing potential; they offered the opinion that sodium valproate is an excellent AED, and may in some cases be the only treatment that can control the patient's epilepsy. They emphasised, however, that sodium valproate should not be used to treat women of childbearing potential without consideration of the possible risks to children conceived in future, and discussion of these risks with the patient.

[127] Morrow, J et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006; 77: 193-198
[128] Meador, K et al. and the NEAD Study Group. Differential and Dose Dependent Effects of In Utero Antiepileptic Drugs. Neurology 2005;64 (Suppl 1):A427

Oct 2005	Published article	*Kini et al.*[129] – This retrospective study, from the Liverpool and Manchester Neurodevelopmental Study Group, found that children exposed to valproate showed distinctive facial features, and that there was a significant correlation between verbal intelligence quotient and dysmorphic facial features. A subtle facial phenotype was also seen in children exposed to carbamazepine. However the authors noted that 45% of unexposed children also had some of the facial features associated with AED exposure, showing that many features may be part of normal variation, and diagnosis of fetal anticonvulsant syndrome is difficult to make on the basis of facial features alone. They concluded by reiterating that developmental surveillance should be offered to children with prenatal exposure to AEDs, particularly those with exposure to high doses of valproate.
Oct 2005	Sanofi written evidence	The applications to amend the data sheets for Epilim were approved by the regulatory authority to incorporate the following wording: ***Pregnancy:*** *Women of childbearing potential should not be started on Epilim without specialist neurological advice.* *Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).* ***Use during pregnancy and lactation:*** *Women of childbearing potential should not be started on Epilim without specialist neurological advice.* *Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.*

[129] Kini, U et al. Dysmorphic features: an important clue to the diagnosis and severity of fetal anticonvulsant syndromes. Arch Dis Child Fetal Neonatal Ed. 2006 Mar; 91(2): F90–F95. Online first October 2005.

		Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate. When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above") ***4.6.1 Pregnancy*** *From experience in treating mothers with epilepsy, the risk associated with the use of Epilim during pregnancy has been described as follows:* *- Risk associated with epilepsy and antiepileptics* *In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy.* *Malformations most frequently encountered are cleft lip and cardio-vascular malformations.* *Epidemiological studies have suggested an association between in-utero exposure to Epilim and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.* ***- Risk associated with valproate*** *In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.* *There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.*

		In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate. *Some data from studies, of women with epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.*
2006	Sanofi written evidence	Cumulative review on Autism, Autism Spectrum Disorders (ASD) and Asperger's syndrome in the PSUR (data lock point 31 January 2006) concluded no causal link established, continue surveillance.
Jan 2006	FDA (USA)	Update to package insert to include a warning about teratogenicity, including neural tube defects.
Aug 2006	Published article	*Meador et al.*[130] – Prospective observational study in USA and UK found more adverse outcomes were observed in pregnancies with in-utero valproate exposure in comparison with other AEDs. Advised that for women who cannot be treated with other AEDs, the dose of valproate should be limited.
March 2007	Published article	*Marson et al* [131]- Unblinded randomised control trial of the effectiveness of valproate, lamotrigine and topiramate for generalised and unclassifiable epilepsy concludes that valproate should remain the drug of first choice for many patients with generalised and unclassified epilepsies. However, due to known adverse effects during pregnancy, the benefits and risks for women in childbearing years should be considered. It noted that the safety of topiramate during pregnancy is unknown.
June 2007	APPG on Epilepsy and Epilepsy Action	'Wasted Money, Wasted Lives'[132] report by the APPG on Epilepsy suggest preconception counselling is added to the NHS Quality and Outcomes Framework (QOF).

[130] Meador, KJ et al. In utero antiepileptic drug exposure: Fetal death and malformations. Neurology: 2006: 67: 407-412

[131] Marson, AG et al (2007) The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. The Lancet 369(9566):1016-1026

[132] Joint Epilepsy Council, APPG on Epilepsy https://www.epilepsy.org.uk/sites/epilepsy/files/images/campaigns/arygrouponepilepsy_wasted_money_wasted_lives.pdf

		Epilepsy Action also presented the case for this indicator to be included at the QOF expert panel in 2007[133].
July 2007	Hansard [134]	[17 July] Debate on 'Epilepsy Services', and on the report 'Wasted Money, Wasted Lives'. The key points from this debate included: • The special needs of women of child bearing potential with epilepsy • Concerns that NICE guidelines have no clout, and awareness they are not being followed • The role of pharmacists in medicine review The response from the Parliamentary Under-Secretary of State for Health, Ann Keen, covered the NICE clinical guidelines, published in 2004, the national service framework for long-term conditions, published in March 2005, and the quality and outcome framework for GPs. A programme of reforms was being undertaken including the choice agenda, payment by results, and practice-based commissioning. Although the Government supported maximising the use of the specialist nurses, they believed that decisions on staffing numbers is best made at the local level.
March 2008	Published article	*Thomas et al* [135] - Prospective study linked to the Kerala Registry of Epilepsy and Pregnancy evaluating mental and motor development of infants of mothers with epilepsy at aged 15 months. Nearly 1/3 of all the infants had impaired mental or motor development. Maternal age, epilepsy type, seizure frequency during pregnancy, and use of folic acid were not found to influence development. Lower development scores were associated with polytherapy and higher dosages. No statistically significant association was found with specific AEDs, although the developmental scores of valproate exposed infants was lower than those exposed to other AEDs. The authors recommended that use of monotherapy and adherence to lower drug dosages are important in the preconception period, as well as during pregnancy, to minimize the risk of developmental impairment in exposed infants.

[133] https://www.epilepsy.org.uk/news/news/new-quality-and-outcomes-framework-indicator-epilepsy-care-great-britain
[134] Hansard. 17 July 2007. Volume 463. Epilepsy Services. Debate in Westminster Hall. http://bit.ly/2MQzZEd
[135] Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav 2008 Jul; 13(1): 229-36

Jul & Oct 2008	Sanofi written evidence	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2006 – 31 January 2007/1 February 2007- 31 January 2008. A cumulative review on autism, autism spectrum disorders (ASD) and Asperger's syndrome was performed, from the reports of exposure during pregnancy. The conclusions were: '*According to the National Center for Health Statistics, the prevalence of autism ranges from around 10 to 15 cases per 10,000 populations. It is noteworthy that a statement is present in the CSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient. No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company*.'
Aug 2008	Published article	*Nicolai et al.*[136] – The authors reviewed 56 studies on antiepileptic drugs and teratogenic effects with a view to considering the association with neurodevelopmental effects. They found that a major problem in the field was methodology, particularly complicating confounding factors. The authors suggested a number of guidelines for future studies on behavioural teratogenicity.
Dec 2008	Published article	*Bromley et al.* [137] – Publication of preliminary results of a prospective study, based on a relatively small sample size for each of the groups. The findings suggested an increased incidence of autism spectrum disorders in children who had been exposed to valproate in utero as compared with a control group. *Bromfield et al* [138] - Use of North American Antiepileptic Drug Pregnancy Registry data to examine role of genetic basis for epilepsy in anticonvulsant teratogenicity. In this relatively small sample (284 valproate-exposed pregnancies in total), the trend was toward increased malformation risk with higher valproate doses, rather than the underlying genetic syndrome. The authors conclude that valproate, and not the underlying genetic syndrome, seems to be associated with the elevated risk for malformations in the drug-exposed foetus.
Feb 2009		Depakote licenced for treatment of manic episode in bipolar disorder.

[136] Nicolai, J., et al. Neurodevelopmental delay in children exposed to antiepileptic drugs in utero: A critical review directed at structural study-bias. Journal of the Neurological Sciences 2008; 271(1): 1-14.
[137] Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology 2008; 71(1-2): 1923-1924
[138] Bromfield, EB et al. Valproate teratogenicity and epilepsy syndrome. Epilepsia. 2008; 49(12):2122-4

March 2009	Hansard	[02 March][139] Question about the amount paid in benefits in relation to children diagnosed with foetal anti-convulsant syndrome following in-utero exposure to sodium valproate. The answer stated that no estimate has been made of this, but that disabilities associated with this syndrome may mean that a child could be entitled to disability living allowance depending on their needs. [03 March][140] Written question on the number of children and adults diagnosed with foetal anti-convulsant syndrome (FACS) resulting from in-utero exposure to sodium valproate. The response stated that no data for the number of people diagnosed with FACS (from exposure to any AED) was available, however studies suggest that incidence of birth defects in babies exposed to AEDs in-utero is 2-3 times higher than the background rate for the general population. It drew attention to the UK Epilepsy and Pregnancy Register, encouraging people to enrol, and stated that findings in 2005 '*suggested that almost 96 per cent. of live-births born to women with epilepsy did not have a major birth defect',* and risks are increased with polytherapy. The response also stated the specific risks known to be associated with sodium valproate, and drew attention to information and advice included in the SmPC and the PIL, and to the NICE guidelines information on epilepsy in pregnancy.
Apr 2009	Published article	*Meador et al* [141] - Prospective, observational, multicentre study in UK and USA ('NEAD study') looking at neurodevelopmental outcomes – interim report. At 3 years, children exposed to valproate in utero had lower IQ scores than those exposed to other AEDs, (9 points lower than those exposed to lamotrigine). The association between valproate and IQ was dose dependent.

[139] Hansard. 02 March 2009. Volume 488. Social Security Benefits. http://bit.ly/35isYCf
[140] Hansard. 03 March 2009. Volume 488. Foetal Anti-convulsant Syndrome. http://bit.ly/2PHohxO
[141] Meador KJ et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605

Apr 2009	Sanofi written evidence	Sanofi submitted an application for a marketing authorisation variation to the MHRA to update the SmPC to include a warning that autism spectrum disorders had been reported in children exposed to valproate in utero. This application was based on a cumulative review of the safety data collected in Sanofi's global electronic pharmacovigilance database and a review of the scientific literature. The conclusion of the review was that some data were available on autism in children after maternal exposure to valproate but there was currently limited information in relation to a causal relationship. The following wording was approved the following year (1 October 2010.) *Section 4.4* *Special warnings: Women of childbearing potential (see section 4.6): A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child . This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation).* *Precautions: Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).* *Section 4.6* *Women of childbearing potential should not be started on Epilim without specialist neurological advice.* *Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.*

		Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. *If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.* *When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")* ***Risk associated with epilepsy and antiepileptics*** *In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.* *No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.* *Antiepileptic drugs should be withdrawn under specialist supervision.* ***Risk associated with valproate*** *In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.* *There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.* *In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.*

		Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy. *Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.* *Autism spectrum disorders have also been reported in children exposed to valproate in utero.* ***In view of the above data*** *When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy.* *Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.*

		The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels. *During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk.* *Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).* ***Risk associated with seizures*** *During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular Risk of death for mother and the unborn child.*
Apr 2009	Netherlands Regulatory Authority (MHRA written evidence)	A referral to the EMA's Committee for Medicinal Products for Human Use ("CHMP") under Article 31 of Directive 2001/83/EC was initiated by the Netherlands regulatory authority because of concerns relating to the efficacy of using valproate containing medicinal products in the acute treatment of manic episodes and the prevention of recurrence of mood episodes in patients with bipolar disorder.
April 2009	Published article	*Harden et al* [142] - Evidence based review (part of a Special Report on Management issues for women with epilepsy). This advised that valproate and AED polytherapy should be avoidable if possible during the first trimester to reduce the risk of major congenital malformations, and throughout pregnancy to reduce the risk of cognitive effects. Additionally, avoidance of phenytoin and phenobarbital may also be considered throughout pregnancy, to reduce cognitive effects on the foetus.

[142] Harden CL, et al; American Academy of Neurology; American Epilepsy Society. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009; 50(5): 1237-46.

Sep 2009	Published article	*Bromley et al.*[143] – Review of large prospective cohort studies. Identify accumulation of evidence of risk for cognitive and behavioural difficulties in children exposed to sodium valproate in utero, and less certain risks with phenobarbital and phenytoin exposure.
Dec 2009	FDA (USA)	FDA published information for healthcare professionals[144] regarding the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to sodium valproate. This advised that healthcare practitioners should inform women of childbearing potential about these risks, and consider alternative therapies, especially if using valproate to treat migraines or other conditions not usually considered life-threatening. Women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant.
Feb 2010	Hansard [145]	[26 Feb] Written question about in-utero effects of sodium valproate. No new information provided.
May 2012	USA	Around 40 individuals filed a lawsuit in the Southern District of Illinois against Abbot Laboratories, claiming that Abbott failed to fully research the potential side-effects of Depakote and adequately warn of the risk of birth defects. These cases were consolidated into a multidistrict litigation (MDL) in January 2012, and by August 2017 there were 129 pending cases with approximately 698 plaintiffs. A “bellwether" approach was taken – the first of which found Abbott not liable, and the second which awarded $38m for failure to warn. This was later appealed, and upheld. In 2018 an order was issued staying all pending Depakote cases.[146]

[143] Bromley, R, Baker, G & Meador, KJ. Cognitive abilities and behaviour of children exposed to antiepileptic drugs in utero. Curr Opin Neurol. 2009; 22(2):162-6. doi: 10.1097/WCO.0b013e3283292401

[144] http://web.archive.org/web/20091207121432/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm192645.htm

[145] Hansard. 26 February 2010. Volume 506. Sodium Valproate. http://bit.ly/2PIfKL5

[146] Macloed, S and Chakraborty, S. Pharmaceutical and Medical Device Safety: A Study in Public and Private Regulation. 2019. HART publishing. Bloomsbury publishing.

July 2010	Published article	*Bromley et al*[147] - Prospective observational control study. Children assessed at less than 2 years. Children exposed to sodium valproate had an increased risk of delayed early development in comparison to the control children (29% of this cohort fell below the average range, compared to 8% of the control group). The authors note that 14% of the cohort were reported as part of the NEAD study (Meador et al., 2009), and the young age of the children. The cohort were followed until the age of 6 (see footnote for details).[148]
Aug 2010	CHMP	CHMP Referral was ended in August 2010 (EC Decision) with the following outcome: Positive benefit-risk ratio in the indication '*Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to the medicinal product for acute mania*' subject to amendments to the Product Information.

Oct 2010	Hansard [149]	[12 Oct] Debate on 'Epilepsy Services'. Key points raised included:
		• "Postcode provision" of services, and epilepsy as an insufficiently understood condition (despite numbers affected)
		• Lack of information/data on various aspects of epilepsy
		• Data being collected by NHS (as a result of other processes) but not used
		• Discussion of key issues around epilepsy:
		  ○ misdiagnosis, poor quality treatment (trial and error with drugs), both leading to poor outcomes;
		  ○ lack of GP expertise/interest;
		  ○ transition from paediatrics to adult services;
		  ○ concerns raised specifically about GPs advising women of childbearing potential.

[147] Bromley R et al. Early cognitive development in children born to women with epilepsy: A prospective report. Epilepsia 2010; 51(10): 2058-2065

[148] The cohort based at the Liverpool and Manchester Neurodevelopment Group were followed up in a number of publications including:
Baker, GA et al. (2015). "IQ at 6 years after in utero exposure to antiepileptic drugs: A controlled cohort study." Neurology 84(4): 382-390.
Some of this cohort also participated in the NEAD study which gathered data from 25 epilepsy centres in the UK and the USA. For example see Meador et al. 2013 (appears in this timeline at January 2013)

[149] Hansard. 12 October 2010. Volume 516. Epilepsy Services. Debate in Westminster Hall. http://bit.ly/2NK8YSC

		The response from the Minister focussed on how the NHS reforms, as set out in the White Paper[150], could resolve some of the issues raised. The Government supported the National Service Framework for Long-tern Neurological Conditions, and the NICE Clinical Guidelines on epilepsy, but believed that implementation is the key issue. In his answer, the Minister expresses the intention of the new Outcomes Framework to improve service design and performance management. The proposals also included a National Quality Board which would be responsible for considering quality standards. Mr Burstow also described the collection and use of data to improve standards, and to enable patients to make decisions about their care. In response to the question regarding information for women of child-bearing age, Mr Burstow raised the proposed indicator under for the Quality and Outcomes Framework for the year 2011-12. In addition, he described how the NHS Commissioning Board will improve epilepsy services.
Oct 2010	Legal	In October 2010, three weeks before the FAC Litigation was scheduled to begin a six month listing in the High Court in London, the Legal Services Commission terminated the funding for the case. As a result, Irwin Mitchell, the solicitors representing the families involved in the FAC Litigation advised discontinuance.
Nov 2010	Valproate Victims	Justice for FACS Kids group started. This group is now known as Valproate Victims UK.
Nov 2010	Hansard	[17 Nov][151] Early Day Motion tabled on 'Withdrawal of Legal Aid for Epilepsy Drug Court Case'. '*That this House notes with regret the decision of the Legal Services Commission to withdraw funding from the claimants in the Fetal Anti-Convulsant Litigation; further notes that the Legal Services Commission first tried to withdraw funding in 2008 but that the decision was reversed when faced with a judicial review; further notes that the withdrawal of this funding is likely to lead to the abandonment of the current action with the result that the claims will then fall outside the 10 year limitation rule; regrets that key evidence around this issue will then remain confidential; strongly regrets the lost opportunity for the parents and children to have the facts and responsibilities in the case decided in open court; and calls on the Government to urge the Legal Services Commission to reconsider its decision to withdraw legal aid funding.*'

[150] Equity and Excellence: Liberating the NHS. White Paper July 2010.
[151] Hansard. 17 November 2010. 2010-12 Session. EDM #1035. Withdrawal of Legal Aid for Epilepsy Drug Court Case. https://edm.parliament.uk/early-day-motion/42024

		[30 Nov] [152] Debate in the Lords on 'Provision of Epilepsy Services'. Key points raised include: • Lack of specialist services - many not seen by epilepsy specialist, and difference between that and being seen by a general neurologist; • The withdrawal of legal aid; • Warnings about sodium valproate • A request for MHRA to review guidance on valproate • The support and role of carers; • 10 'levers' which would improve services for young people with epilepsy; • Care for women with epilepsy who are pregnant/or prior to pregnancy; • Failure of trusts to adopt the NICE guidelines; • Local funding cuts impacting on ability to deliver specialist services such as those which support families with epilepsy Baroness Northover responded on behalf of the Minister for Health. The response repeated the points made in the Commons in October, regarding how the proposed reforms in the NHS White Paper could help deliver improvements to services, through effective commissioning, use of data, and providing information and choice for patients. She also stated that Paul Burstow (Minister for Health) would be meeting the epilepsy charities to discuss the new agenda. In relation to sodium valproate, the Baroness stated that they were acutely aware of the situation of the families, and that she would take the idea of reviewing this back to the Department.
Nov 2010	Sanofi written evidence	Sanofi's application for a variation to update the SmPC for Depakote in line with the Article 31 referral outcome from 26 August 2010 was approved.
2011	FACT	Fetal Anti-Convulsant Trust (FACT) launched.
April 2011	Numerous sources	Quality and Outcomes Framework includes an indicator for pre-conception counselling, providing an incentive to GPs, stating: '*Women taking AEDs receive vital pre-conception counselling.*'

[152] Hansard. 30 November 2010. Volume 722. Provision of Epilepsy Services. Debate in Lords Chamber. http://bit.ly/2NVtxvc

Mar 2011	Published article	*Cummings et al* [153]- Observational cohort study recruited from the UK Epilepsy and Pregnancy Register, of children aged 9 – 60 months. In utero exposure to sodium valproate and carbamazepine was associated with developmental delay. 39.6% of children exposed to sodium valproate in utero had mild or significant developmental delay.
June 2011	FDA (USA)	US FDA warned of the possibility of impaired cognitive development in children born to mothers exposed to valproate in utero. As in the EU they advised women of child bearing potential should be counselled about the risks, advised of the need for contraception, and that alternative medicines should be considered[154].
Jun 2011	Sanofi written evidence	Sanofi reviewed the CSI in February 2011, alongside other recommendations, and considered that further advice should be added to the SmPC regarding contraception. The application was submitted to the MHRA in June 2011, and the variations below approved in July 2011. *Section 4.4* *Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women (sic) of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.* *Section 4.6 - Update below categories and the remaining text remains as it is.* *Risk associated with valproate* *In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.* *There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.*

[153] Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child. 2011 Jul;96(7):643-7.
[154] https://www.fda.gov/Drugs/DrugSafety/ucm261543.htm

		In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. *Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.* *Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy* *Autism spectrum disorders have also been reported in children exposed to valproate in utero.* *<u>In view of the above data</u>* *The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women (sic) of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.* *If a women (sic) plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication:*

		• *In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.* • *In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.* • *Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.* *The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.* *Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).*
July 2011	Published article	*Tomson et al* [155] - EURAP epilepsy and pregnancy registry analysis found an increase in malformation rates with increasing dose at conception for all drugs. The risk of malformations was higher with a parental history of major congenital malformations. The lowest risks were found in lamotrigine (<300mg/d) and carbamazepine (<400 mg/d). Risks were significantly higher with sodium valproate and phenobarbital at all doses, and carbamazepine at doses >400 mg/d.
Nov 2011	Hansard	[29 Nov] Debate on Epilepsy[156] – key points included: • inadequate/patchy provision of epilepsy services; • importance of epilepsy nurses in providing structured follow-up information following initial diagnosis/consultation; • the transition from childhood to adult services; • failure to follow NICE guidelines;

[155] Tomson, T et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011; 10(7):609-17.
[156] Hansard. 29 November 2011. Volume 536. Epilepsy. http://bit.ly/2zR66v2

		• the move to emphasis on local services/needs/structure, and the opinion that rarer conditions such as epilepsy requiring a national strategy instead The Minister for Health (Paul Burstow) provided updates on improvements to commissioning of epilepsy services, and the role of the NHS Outcomes Framework, following on from his response in October 2010. On the 8th December, another debate on 'Neurological Conditions'[157] draw attention to the lack of access to services for diagnosis of young people with epilepsy; epilepsy as a 'Cinderella' condition with high levels of mortality; and quality standards referred to NICE. Under-Secretary of State for Health, Earl Howe gave a response focussing on reforms to commissioning and quality standards. The following year [20 Nov][158] another debate on the subject again draw attention to concerns about current/future specialised services for epilepsy, that current services were not close to NICE guidelines; and the impact of cuts to services. Again, the need for commissioning of specialised services was raised. Baroness Northover responded drawing attention to the Governments's response to the report of the Public Accounts Committee on neurological services,[159] the need for better integration of health and social care, and the Health and Social Care Act 2012. Examples of action include: establishment of four new strategic clinical networks, work with neurological organisations regarding specialised commissioning and data, and upcoming quality standards for the diagnosis of epilepsy.

[157] Hansard. 8 December 2011. Volume 733. Lords Debate. Health: Neurological Conditions. http://bit.ly/32ZR2YM
[158] Hansard. 20 November 2012. Volume 740. Lords Debate. Health: Neurological Services. http://bit.ly/34a0Wat
[159] National Audit Office. Services for People with neurological conditions. 16 December 2011.

Jan 2012	NICE	Updated clinical guidelines 'CG 137 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' were published. These guidelines contain specific warnings in relation to women and girls of childbearing potential and instructions regarding preconception counselling, e.g.: **(p11) Special considerations for women and girls of childbearing potential** Women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children, breastfeeding and menopause. [2004] **1.9 Pharmacological treatment** The GDG is also aware of specific issues with prescribing sodium valproate to girls and women of childbearing age. Recommendations in this section offer alternative prescribing options for this group… 1.9.1.10When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. [new 2012] **1.15 Women and girls with epilepsy** This section contains extensive information for healthcare professionals under the following headings, which include general advice regarding all women and girls of childbearing potential on AEDs, as well as specific warnings in relation to valproate: • **1.15.1 Information and advice for women and girls with epilepsy** *'1.15.1.4…Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. [new 2012]'* • **1.15.2 Contraception –** discusses possibility of interaction of AEDs with different oral contraceptive methods,

		• **1.15.3 Pregnancy –** discuss risks with those who plan to stop medication, encourage to notify the UK Epilepsy and Pregnancy Register, discuss relative benefits of risks of adjusting medication, discuss risks of seizure, discuss risks of complications, offer high-resolution ultrasound for structural anomalies, genetic counselling, use lowest effective dose of AED • **1.15.4 Breastfeeding –** '*breastfeeding for most women and girls taking AEDs is generally safe and should be encouraged'*, but notes that each mother should be supported in her choice, and prescribers should consult individual advice in the SmPC and BNF. • **1.15.5 After the birth –** HCPs should discuss with soon-to-be and new parents simple safety precautions to reduce risk of accidents and ensure maximum safety for both mother and baby.
March 2012	Denmark (MHRA written evidence)	Denmark presented a summary of the most recent data on the neurodevelopmental effects of in utero exposure to valproate to the EU Pharmacovigilance Working Party (PhVWP). In the UK, this subject generated significant parliamentary and media interest. During 2012/13 the MHRA was contacted on multiple occasions by several contacts in patient support groups calling for action to update warnings and issue further communications.

Aug 2012	Sanofi written evidence	Sanofi submitted an application to the MHRA to update the SmPC to include dose-effect for congenital malformations. This was based on a safety review carried out by Sanofi on published articles, the result of which suggested that the overall incidence of congenital malformations in children born of women with epilepsy is approximately threefold that of healthy women. The risk was elevated for all AED monotherapy and further elevated for AED polytherapy compared to women without epilepsy. The risk was significantly higher for children exposed to valproate monotherapy and to polytherapy of 2 or more drugs when the polytherapy combination included phenobarbital, phenytoin, or valproate. It concluded that further research is needed to delineate the specific risk for each individual AED and to determine underlying mechanisms including genetic risk factors. Analysis of the Sanofi pharmacovigilance database was also undertaken, which showed a dose-effect of valproate on congenital malformation. This was supported by the review of the available literature sources.[160] The CSI was updated to reflect this.
Nov 2012	Sanofi written evidence	The SmPC was updated to reflect these findings, approved in November 2012. *Section 4.6 - Update below categories and the remaining text remains as it is.* *Risk associated with valproate* *In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.* *There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.* *In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate.*

[160] See page 39 of Sanofi timeline for full list of literature sources used in this review.

		The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73% (95% CI: 8.16 – 13.29). Available data indicate dose dependency of this effect. *Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.* *Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.* *Autism spectrum disorders have also been reported in children exposed to valproate in utero.*
Nov 2012	FACSA	FACS Association was established in November 2012.
Nov 2012	INFACT	Independent Fetal Anti Convulsant Trust (IN-FACT) formed in November 2012.
Jan 2013	Published article	*Meador et al.* [161] – 'NEAD study' – Prospective observational study – Follow up at 6 years, found that foetal valproate exposure has dose-dependent associations with reduced cognitive abilities. Effects include reduced IQ, verbal and memory abilities compared with other antiepileptic drugs, and worsened non-verbal and executive functions compared with lamotrigine.

[161] Meador KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52

		Further outcomes from the NEAD study were published in September 2013[162] focussing on adaptive and emotional/behavioural functioning. The results showed that children whose mothers took valproate during pregnancy had significantly lower adaptive scores than he lamotrigine and phenytoin groups, were rated by their parents as exhibiting significantly more atypical behaviours and inattention, and were at a significantly greater risk for a diagnosis of ADHD. The authors recommend that these risks are communicated to women who require antiepileptic medication. They also highlight the need for additional research with large study samples. *Bromley et al.*[163] - Prospective cohort control study. Children followed until 6 years of age. An increased risk of neurodevelopmental disorders was found in children exposed to monotherapy and polytherapy sodium valproate in utero, compared with control children. Autistic spectrum disorder was the most frequent diagnosis. No significant increase was found among children exposed to carbamazepine or lamotrigine.
Mar 2013	Hansard [164]	[26 March] Debate on 'Fetal Anti-convulsant Syndrome' – this gave a recap of the main issues that had been previously raised. It asked about what would be done to support children affected and ensure women that are informed of risks. The response from the Parliamentary Under-Secretary of State for Health, Anna Soubry, summarised the known risks of pregnancy in women with epilepsy, including exposure of the fetus to anti-epileptic drug, and concerns that women have not had sufficient explanation in order to make an informed choice before and during pregnancy. She outlined the NICE guidelines, and that MHRA regularly reviews the evidence on AEDs and the information in patient information and product leaflets. The response stated that better care and outcomes for disabled children are a priority of the Government, and this is supported through the new Children And Young People's Health Outcomes Board and Health Outcomes Forum. Services for children with special educational needs will be enhanced by provisions in the Children and Families Bill.

[162] Cohen, MJ et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. Epilepsy & Behaviour 2013: **29**(2): 308-315.
[163] Bromley, RL et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. Journal of Neurology, Neurosurgery & Psychiatry 2013;84:637-643.
[164] Hansard. 26 March 2013. Volume 560. Fetal Anti-convulsant Syndrome. Debate in Westminster Hall. http://bit.ly/2N1BPlZ

April 2013	Published article (Denmark)	*Christensen et al*[165] - Population-based study (Denmark). This study was able to adjust for maternal epilepsy, and found maternal use of valproate during pregnancy was associated with significantly increased risk of autism spectrum disorder and childhood autism.
May 2013	FDA (USA)	FDA Safety announcement based on the final results of the NEAD study, advising healthcare professionals that valproate is contraindicated for the prevention of migraines in pregnant women.[166] This was due to evidence that they can cause decreased IQ scores in children whose mothers took them whilst pregnant. Stronger warnings about use during pregnancy were added to the drug labels, and valproate's pregnancy category for migraine use was later changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug). Valproate products remained category D for the treatment of epilepsy and bipolar disorder. For women of childbearing age who are not pregnant, valproate should not be taken unless essential to the management of the medical condition. Those taking valproate should use effective birth control.
July 2013		Panorama episode "The Truth about Pills and Pregnancy"[167] airs, including a section on Fetal Valproate Syndrome.
Oct 2013	MHRA written evidence	A Pharmacovigilance Expert Advisory Group conducted a full literature review of longer term neurodevelopment effects following foetal valproate exposure.[168] On their advice, MHRA made a referral under Article 31 of Directive 2001/83/EC for valproate for the treatment of epilepsy,[169] which requested that the Pharmacovigilance Risk Assessment Committee gave its recommendation on whether new data on teratogenic effect impacts the balance of benefits and risks of valproate in all of its authorised indications and whether marketing authorisations should be maintained, varied suspended or withdrawn.
Oct 2013	DH (MHRA written evidence)	Minister met a delegation led by Anas Sarwar MP to discuss Fetal Anti-Convulsant Syndrome (FACS). Alec Shelbrooke MP, Chair of the All-Party Group on Thalidomide, was also present, with a number of affected parents representing the various support groups and a young person who is herself affected by FACS.

[165] Christensen, J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013 Apr 24;309(16):1696-703. doi: 10.1001/jama.2013.2270
[166] FDA Safety Announcement 05 06 2013 http://www.fda.gov/drugs/drugsafety/ucm350684.htm
[167] https://www.bbc.co.uk/programmes/b036fddg
[168] MHRA evidence: **(Minutes in PDF annex doc 'J. PEAG mins October 2013')**
[169] https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-notification_en.pdf

Nov 2013	MHRA written evidence	MHRA Drug Safety Update[170] contained advice '*Sodium valproate: special reminder on risk of neurodevelopmental delay in children following maternal use – not for use in pregnancy unless there is not effective alternative'.*
Jan 2014	DH (MHRA written evidence)	DH hosted meeting on prescribing of Anti-Epileptic drugs to pregnant women. Attendees included MHRA, Royal Pharmaceutical Society, the National Clinical Director for Neurological Conditions and a pharmacist from Maternity Services at Guys and St Thomas's Hospital. A submission was made to update Ministers on action being taken to improve awareness of risks of prescribing AEDs to pregnant women.
Feb 2014	MHRA written evidence	First meeting of the CHM Sodium Valproate Working Group. Advice sought in relation to ongoing EU review.[171]
Feb 2014	NICE	'Evidence Update 53: A summary of selected new evidence relevant to NICE clinical guideline 137 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' This updated some specific areas of advice including: **Women and girls with epilepsy** • **In utero exposure to AEDs and risk of congenital malformations** Among women who take AEDs, particularly sodium valproate, during pregnancy, those who have children with congenital abnormalities are at higher risk of having fetal malformations in subsequent pregnancies exposed to AEDs than women whose first pregnancies did not result in fetal malformations. • **In utero exposure to AEDs and cognitive outcome** Limited evidence suggests that compared with other AEDs, sodium valproate during pregnancy has a negative, dose- dependent effect on long-term cognitive outcomes in offspring. Periconceptional folic acid may lessen the effect of AED use during pregnancy on the child's intelligence quotient (IQ). • **Breastfeeding**

[170] MHRA Drug Safety Update. Volume 7, Issue 4. November 2013. https://webarchive.nationalarchives.gov.uk/20150110161436/http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con336729.pdf

[171] MHRA written evidence to the Review – minutes of CHM sodium Valproate Working Group February 2014

		Limited evidence suggests that AED use while breastfeeding does not affect cognitive outcome in children exposed to AEDs in utero. It referenced the MHRA special reminder on the risk of neurodevelopmental delay, and summarised key findings from the Australian[172] and UK[173] registry studies, and the NEAD study on neurodevelopmental effects of in-utero exposure[174] and breastfeeding[175] to support these updates.
Apr 2014	MHRA written evidence	Yellow Card system updated to collect information about drug exposure in utero.
Apr 2014	Written evidence from patient groups and charities, and MHRA.	The Quality and Outcomes Framework indicator for pre-conception counselling was retired (EP003 'The percentage of women aged 18 or over and who have not attained the age of 55 who are taking AEDs who have a record of information and counselling about contraception, conception and pregnancy in the preceding 12 months.') Epilepsy Action informed the Review[176] that they met with the BMA in January of 2014, who assured them that GPs would still meet the QOF requirements, despite evidence presented to them that in fact many GPs were failing to meet the requirements and adhere to the strengthened MHRA advice. Epilepsy Action also raised the concern that this contradicted the advice of the NICE QOF advisory committee who advised that the indicator should be retained (with amendment). Partly anticipating the outcome of the EMA review, the MHRA met with various groups, including Epilepsy Action, and started work on guidance for patients and professionals.

[172] Vajda, FJ et al. Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. Epilepsia 2013; 54: 181–6
[173] Campbell, E et al. Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. Epilepsia 2013; 54: 165–71
[174] Meador, KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 2013; 12: 244– 52
[175] Meador, KJ et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 2010; 75: 1954–60
[176] Epilepsy Action written evidence to the Review

June 2014	MHRA written evidence	Sodium Valproate Working Group, 18 June[177] • Considered that it was plausible for sodium valproate to increase the potential for ADHD to occur, but strength of existing evidence for casual relationship was weak. Group recommended investigating use of large Scandinavian observational databases, Clinical Practice Research Datalink, and review of publications on Swedish databases. • Noted no change required in advice regarding dosage and folic acid. • Noted currently no evidence of an adverse effect on infants from maternal use of sodium valproate while breastfeeding, and recommended women should be counselled about the benefits of breastfeeding in light of the data. • Discussed the benefit-risk of sodium valproate in different indications • Noted that the risk of neurocognitive impairment from valproate exposure probably existed throughout pregnancy. • Recommended that in women with epilepsy receiving valproate who experience an unplanned pregnancy, the risk of changing to a different antiepileptic drug should be weighed against the risk of continuing valproate treatment. The Group recommended that the UK Epilepsy and Pregnancy Registry should be reviewed for data on changing AEDs during pregnancy. • Recommended that children exposed in utero to valproate should be referred early for a neurological assessment. • Proposed a number of regulatory actions to minimise risk and ensure patients are informed.
Oct 2014	TGA (Aus)	The Therapeutic Goods Administration, Australia (TGA) reviewed updated information regarding the association between use of valproate during pregnancy and cognitive impairment in children. TGA's review of the updated information in the NEAD study found that the information about cognitive impairment should be updated in the valproate PIL to show that cognitive deficits have been observed at six years of age. This was communicated via a Medicines Safety Update.[178]

[177] MHRA written evidence. Annex L. Commission on Human Medicines, Sodium Valproate Working Group, 18th June 2014.
[178] Medicines Safety Update, Vol. 5, No. 59 https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-5-number-5-october-2014-0

Oct 2014	EMA (PRAC)	The Article 31 referral concluded (9th October)[179] with a finding by the Pharmacovigilance and Risk Assessment Committee ("PRAC") that the benefit-risk balance of valproate remained favourable subject to strengthening restrictions due to the risk of malformations and developmental problems in children exposed to valproate in the womb. *The recommendations include:* • *Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option after trying other treatments, should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.* • *Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.* • *Doctors who prescribe valproate should provide women with full information to ensure understanding of the risks and to support their decisions.* • *Educational materials should be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks.* • *Doctors required to review the treatment of girls and women on a regular basis, including at puberty and when a woman plans to become pregnant.* • *SmPCs and PILs to be updated with the latest information and recommendations.*

[179] Press release (10 October) https://www.ema.europa.eu/en/news/prac-recommends-strengthening-restrictions-use-valproate-women-girls; All documents can be found here: https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances#overview-section. MHRA Press release in response to the PRAC recommendations: https://webarchive.nationalarchives.gov.uk/20141205230802/http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON465926

Oct 2014	ABN written evidence	The Association of British Neurologists[180] (in collaboration with the International League Against Epilepsy) wrote to the MHRA regarding the recommendation from the PRAC, stating their concerns about girls and women not being able to access appropriate treatment, asking for clarification of the recommendation and expressing their disappointment that this announcement had been made without communication with the professional bodies. In a letter to MHRA dated December 2014, the ABN expressed their concerns about the risk form portraying a one-sided risk (i.e. not portraying the risks of inadequately treated epilepsy), interpretation that an alternative medication should be tried before valproate, even when it may be the best drug for the individual, and that '*evidence that valproate is solely responsible for developmental delay remains incomplete and our experts feel that it is presented too strongly as an argument in favour of using alternative agents before valproate'.*
Nov 2014		*Bromley et al* [181] - Cochrane Review which considered all the studies published up to May 2014, to assess the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes. The authors state that the most important finding was the reduction in IQ in the valproate exposed group. However it also noted, that for some women valproate is the most effective drug at controlling seizures, and that to make informed treatment decisions women require detailed counselling. They note that there is insufficient data about newer AEDs and further research is required. Finally they advise that most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.
Nov 2014	EMA	The recommendations made by the PRAC, to strengthen warnings on the use of valproate medicines in women and girls, were adopted by Coordination Group for Mutual Recognition and Decentralised Procedures - Human ("CMDh"), the Group responsible for examining questions related to marketing authorisation of human medicines in two or more EU Member States.

[180] Letters dated October 28th 2014, and 9th December 2014 - see written evidence from ABN.
[181] Bromley, R et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014 Oct 30;(10):CD010236

Nov – Dec 2014	Sanofi written evidence	Sanofi provided a draft 'Dear Healthcare Professional communication' ("DHPC") to MHRA for review and approval. The DHPC was to provide information on the recommendations of the PRAC and the measures put in place following the Article 31 referral. The MHRA responded that the DHPC would be sent by MHRA via the Central Alerting System ("CAS") after consultation with the Commission on Human Medicines ("CHM"). Following a query from Sanofi, the MHRA confirmed that marketing authorisation holders would be required to produce the educational materials recommended by the PRAC, but that the MHRA were seeking input from stakeholders nationally on the wording.

Dec 2014	ANSM (France)	Following reassessment of risk/benefit of valproate and derived products by the EMA, a letter was sent to health professionals, strengthening warnings about the use of valproate.
		• Increased risk of developmental disorders/ congenital malformations.
		• Valproate should not be prescribed unless there is ineffectiveness or intolerance to all other drug alternatives.
		• Treatment should be initiated and monitored by a physician specialised in epilepsy/bipolar disorder.
		• The benefit / risk ratio of valproate therapy should be carefully assessed before the first prescription, as well as at each regular treatment check.
		• You must ensure that all treated patients are informed and have understood:
		  ○ the risks associated with valproate treatment during pregnancy;
		  ○ the need to use effective contraception;
		  ○ the need for regular reassessment of treatment;
		  ○ the need to consult promptly if they are planning pregnancy or pregnancy.

Jan 2015	Published article	Drug Safety Update issued following completion of the European review. The update contained detailed information on risk and set out actions expected of healthcare professionals. In addition, it announced that valproate had become a black triangle medicine indicating that any suspected side effects should be reported via the Yellow Card scheme[182].

[182] Introduced in the UK to highlight medicines subject to intensive safety monitoring, since 2013 the black triangle ▼ has been part of an EU-wide scheme to indicate 'additional monitoring', and that suspected adverse reactions should be reported. Further details can be found on this website.

Jan 2015	Sanofi	Sanofi submitted applications for variations to the marketing authorisations for Epilim and Depakote products to update the SmPCs to implement the PRAC recommendations. The proposed changes for the SmPCs for Epilim products were as follows: *Section 4.2:* *"Female children, female adolescents, women of childbearing potential and pregnant women* *Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses".* *Section 4.4:* *Removed existing text under heading "Women of childbearing potential" (see section 4.6): and added the following text in A text box.* *"Female children/Female adolescents/Women of childbearing potential/Pregnancy:* *Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant.* *Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy (see section 4.6).* *The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.* *In particular the prescriber must ensure the patient understands:*

		• *The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.* • *The need to use effective contraception.* • *The need for regular review of treatment.* • *The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.* *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).* *Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy".* Section 4.4.2 (precautions) was unrevised from previous version *<u>Section 4.6</u>* *"Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.* *<u>Pregnancy Exposure Risk related to valproate</u>* *Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.* *<u>Congenital malformations</u>* *Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.*

		Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. *Developmental disorders* *Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.* *Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.* *Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.* *There are limited data on the long term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.* *Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).* *Female children, female adolescents and woman of childbearing potential (see above and section 4.4)* *<u>If a Woman wants to plan a Pregnancy</u>* • *During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.*

		• *In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed* • *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.* *Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:* • *Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.* • *Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.* • *To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.* *Breastfeeding* *Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. … (see section 4.8). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman".* The variations were approved on 11 February 2015.
Jan 2015	MHRA written evidence	21 Jan - MHRA CAS Alert 'Medicines related to valproate: risk of abnormal pregnancy outcomes'[183] published. This included a letter and guide for healthcare professionals, and a booklet for patients. A supporting article was also published in Drug Safety Updates[184].

[183] https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102287
[184] https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes

Feb 2015	Hansard	[02 Feb][185] Lords Debate on availability and accessibility of new epilepsy medications and treatments. In response to a question about progress in providing advice to women on the use of sodium valproate before and during pregnancy, the Minister responded that this was a big issue for women of child-rearing age, and that she expected that a woman's consultant should advise her on that concern. [26 Feb][186] Commons debate on '*Epilepsy*'. A wide debate, including other side effects of epilepsy medication, and discrimination against those with epilepsy. It also included specific reference to the concerns about in-utero exposure to valproate, including considering a "red flag" system to notify GPs of the risks posed to women of child-bearing age. Teresa Pearce raised questions about compensation and 'justice' for those affected. The Minister of State, Department of Health (Norman Lamb) recognised the concerns about risks to women of child-bearing age, and stated that these have been subject to an EU-wide review. MHRA issued new guidance in January 2015, and the BNF was updated. The Department was considering the introduction of a 'red flag' system to notify GPs of the risks posed to women of child-bearing age. Regarding broader concerns about the provision of epilepsy services, Mr Lamb stated that the Government was committed to high-quality outcomes for people living with epilepsy. The response set out the current provisions in primary and secondary care, a commitment by Health Education England to invest in 217 neurological speciality training places, and to the guidelines set out by NICE.
May 2015	ANSM (France)	Letter sent to doctors detailing changes to prescribing/dispensing of Valproate. • Valproate should not be prescribed except for those for whom alternatives are ineffective or ill-tolerated. • Prescription now restricted to specialists in neurology, psychiatry or paediatrics. • Prescription requires the collection of a care agreement after informing the patient. After a year, reassessment of treatment by a specialist is required. • The benefit / risk ratio of the treatment should be re-evaluated regularly and at least once a year, especially when a young girl reaches puberty, when a woman is planning a pregnancy.

[185] Hansard 02 February 2015. Volume 758. Lords Debate. Epilepsy: New Treatments. http://bit.ly/303XXmh
[186] Hansard. 26 February 2015. Volume 593. Epilepsy. http://bit.ly/2MUa5zg

May-Oct 2015	Sanofi written evidence	A Drug Utilisation Study ("DUS")[187] Protocol was submitted to the EMA on 18 May 2015 on behalf of the consortium of marketing authorisation holders for valproate products, led by Sanofi. Following PRAC's comments, a revised DUS protocol and prescriber survey study protocol were submitted to PRAC on behalf of the MAHs consortium on 29 October 2015.[188]
Jun 2015	Published article	*Tanoshima et al* [189] - Systematic review and cumulative meta-analysis of 59 studies in total, looking specifically at congenital abnormalities. Found significant risk signals emerged: • neural tube defect – 1992 • genitourinary and musculoskeletal abnormalities – 2004 • cleft lip and/or palate – 2005 • congenital heart defects - 2006
Jul 2015		APPG on Anti-Epileptic Drugs in Pregnancy set up with Teresa Pearce MP as Chair. Prior to this it was part of the APPG for Harmful Drugs with the Thalidomide Group (2014), with Alec Shelbrooke acting as chair. In September 2016 Norman Lamb took on the Chairmanship and the APPG was renamed Valproate and other Anti-Epileptic Drugs in Pregnancy.
Jul-Dec 2015	Sanofi/MHRA written evidence	Correspondence between MHRA and Sanofi on the development of further educational materials and risk minimisation tools following the PRAC recommendations. These materials were reviewed by the Valproate Stakeholder network.
Sept 2015	New Zealand	New Zealand 'Medsafe' - Alert Communication – Sodium valproate contraindicated in pregnancy due to risk of congenital malformations and developmental delay, as well as risk of autism.
Oct 2015	MHRA written evidence	First Valproate Stakeholder Network meeting – The aim of the meeting was to agree measures to drive forward compliance with prescribing restrictions for sodium valproate and ensure that women treated with valproate are fully aware of the risks in pregnancy.
Dec 2015	MHRA written evidence	Stakeholder Network meeting – The meeting discussed proposals from Sanofi for a package label warning and patient card to be distributed by pharmacists. The proposals were endorsed in principle. The other strand of work involves alerts on GP IT systems and this is running to a longer time frame. NHSE and HSCIC colleagues tasked with taking this forward.

[187] Ongoing study - http://www.encepp.eu/encepp/viewResource.htm?id=15802
[188] Note: Drug utilisation studies (DUS) describe how a medicinal product is prescribed and used in routine clinical practice in large populations.
[189] Tanoshima, M et al. Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. Clinical Pharmacology and Therapeutics 2015; 98(4): 417-441 https://doi.org/10.1002/cpt.158

Jan – Feb 2016	Written evidence from MHRA, Sanofi	MHRA, Sanofi and Valproate Stakeholder network develop the UK specific educational materials – HCP and Patient Booklet, Patient Card and Discussion of Risk form. The wording was also agreed for an outer carton warning for women.
Feb 2016	Written evidence from MHRA, NICE	A valproate 'Toolkit' was launched by the MHRA on the 8th February.[190] This included information for patients in the form of a patient card and information leaflets, and for healthcare professionals in the form of leaflets, a prescriber checklist and a video. The hardcopy materials were mailed by Sanofi between 8-19 February 2016. NICE also updated their epilepsy guideline in February 2016 to link to the MHRA's Toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy.[191]
Feb 2016	France	Feb 2016 – IGAS Report – 'Investigation of proprietary medicinal products containing sodium valproate'[192] – found a lack of response to the teratogenic risk of valproate by both the health authorities and the principal marketing authorisation holders. Following this, the Director General of Health and of the ANSM presented a plan of action. In November of that year, the French Parliament voted to create nationwide compensation fund (initial E10m) for claims relating to valproate use in pregnancy
Feb 2016	ABN	ABN made a Statement on Sodium Valproate taken in Pregnancy[193] which advised their members and general readership on the risks of becoming pregnant while taking this medication, as well as the risks of changing medication (no certainty as effective a treatment; increased risks if not as effective; advised not to drive for six months). In also raised the issue that while young men can benefit from valproate, young women must "*first try less effective or less proven treatments for their epilepsy*".
May 2016	MHRA/ Sanofi/ RCPCH written evidence	MHRA, Sanofi and Dr Dan Hawcutt (Royal College of Paediatrics and Child Health) met to discuss child specific valproate educational materials. Dr Hawcutt raised concerns that clinicians felt that the current toolkit was not appropriate for children and their families, and that the pregnancy message was not relevant at that point in time. It was agreed that RCPCH would produce draft materials and share with MHRA.

[190] https://webarchive.nationalarchives.gov.uk/20170517234711/https://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients.
The video can be seen here: https://youtu.be/MNv-BG-bgF0

[191] https://www.nice.org.uk/guidance/cg137

[192] http://www.igas.gouv.fr/IMG/pdf/2015-094R.pdf

[193] ABN Statement on Sodium Valproate taken in Pregnancy - Feb 2016; ABN Statement on Sodium Valproate taken in Pregnancy - Feb 2016 (for general readership)

June 2016		Label warning on the outer packaging of valproate products began appearing in pharmacies from June 2016.
Oct 2016	Epilepsy charities	October 2016 – Epilepsy Action, Epilepsy Society and Young Epilepsy survey found that only 20% of women taking sodium valproate know the risks, 20% of women taking sodium valproate did not know the risks and 27% of those taking sodium valproate had not had a discussion about pregnancy with a healthcare professional. This survey was repeated in 2017.
Nov 2016	Published article	*Weston et al* [194]- Cochrane Review. Children exposed to valproate in utero had the highest level of risk of a malformation, and this risk was dose-dependent. Based on available evidence, levetiracetam and lamotrigine appeared to be associated with the lowest level of risk, but more data is required. *Choi et al* [195] - Animal studies using the valproate model of autism spectrum disorder suggests transgenerational effects.
Nov 2016	France	The French parliament voted to create a compensation fund for those affected by valproate.[196]
Jan 2017	Sanofi	Sanofi made an application to MHRA to add the pictogram to the Epilim outer carton. User Testing of the Pictogram had been conducted by Sanofi and the user test report was submitted as part of the application. This application was subsequently put on hold by MHRA to await outcome of the new Article 31 referral that was announced in March 2017.
Jan 2017	Sanofi and other manufacturers	Sanofi and other companies included in the MAH consortium submitted the first interim database study report of "A joint Drug Utilisation Study (DUS) of valproate and related substances in Europe using database", for a PRAC review. The preliminary conclusions were that the number of women of child-bearing potential using valproate had decreased in Sweden, Germany, France, Spain and UK after implementation of the risk minimisation measures. However, the preliminary data, suggested that there was no evidence of improved prescribing behaviour after implementation of these risk minimisation measures.

[194] Weston, J et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11:CD010224.
[195] Choi, CS et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. Scientific Reports (Nature) 2016; 36250; doi: 10.1038/srep36250
[196] Information the scheme can be found here: https://www.oniam.fr/valproate

		A survey among psychiatrists, neurologists and GPs[197] indicated that 40% of the participating HCPs stated that they did not recall receipt of either the 'Dear Healthcare Professional' letter or the educational materials. A large number of participating HCPs were unaware of the current prescribing conditions indicating a need for further improvement.
Feb 2017	MHRA and Sanofi written evidence	MHRA and Sanofi discussed the lack of evidence of impact of the action taken to date, and that further actions were necessary.
Feb 2017	France	ANSM requested to contraindicate the use of valproate products in bipolar disorder in pregnant women pending the outcome of the referral.
Mar 2017	France	The French regulatory authority, ANSM, initiated an Article 31 referral of valproate medicines to consider the effectiveness of the risk minimisation measures put in place following the 2014 referral and to consider whether further EU-wide action should be recommended to minimise the risks in women who are pregnant or of childbearing age.
April 2017	France	Apr 2017 – French National Agency for the Safety of Medicines (ANSM) and National Health Insurance Administration Report on Valproate use in pregnancy[198]. This study found a teratogenic risk of valproate consistent with the literature, and notes that the risk of congenital malformation is lower for other drugs for the treatment of epilepsy and bipolar disorder, although notes that these results should be interpreted with caution.
April 2017	MHRA	MHRA release Patient Safety Alert: '*Resources to support the safety of girls and women who are being treated with valproate*'.[199] This provided updates on the valproate toolkit. The actions in this alert asked all organisations to undertake systematic identification of girls and women who are taking valproate, and ensure the MHRA resources are used to support them to make informed choices.

[197] Study page: http://www.encepp.eu/encepp/viewResource.htm;jsessionid=xMAzioiZQUT7Z6NIznaeykMPbzIyaJPJvKpIgpoyogaYAeWp1lPz!310772498?id=19975
Paper: "Evaluation of the effectiveness of risk minimisation measures: a joint PASS survey among health care professionals to assess their knowledge and attitudes on prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom": http://www.encepp.eu/encepp/openAttachment/studyResult/23394

[198] https://ansm.sante.fr/S-informer/Communiques-Communiques-Points-presse/Malformations-congenitales-chez-les-enfants-exposes-in-utero-au-valproate-et-aux-autres-traitements-de-l-epilepsie-et-des-troubles-bipolaires-Communique

[199] https://improvement.nhs.uk/documents/911/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf

July 2017		Veroniki et al [200] [201] - Two systematic reviews into major congenital malformations and neurological development in children exposed to anti-epileptic drugs in utero. The following AEDs were associated with a higher risk of congenital malformations: ethosuximide, valproate, topiramate, phenobarbital, phenytoin, carbamazepine. The newer generation AEDs, lamotrigine and levetiracetam were not associated with a higher risk compared to control. Valproate was the only AED significantly associated with developmental delay. However oxcarbazepine, valproate, lamotrigine, and lamotrigine+valproate were associated with significantly greater odds of developing autism compared with control. Increased risk of psychomotor delay was found with valproate, and polytherapy of carbamazepine, phenobarbital and valproate.
Sep 2017	EMA	The EMA held a Public Hearing to consider valproate,[202] which heard from patient representatives, carers and their families, healthcare professionals and academia, as well as from Sanofi. The families spoke powerfully about the impact of valproate on those affected. Most speakers raised the issue that the information resources were still not reaching the right people at the right time. Speakers provided important suggestions on how dissemination of information could be improved including; messaging on packaging, prompts in prescribing and dispensing software, women on long-term valproate to be reviewed at least annually, record of women receiving appropriate counselling, registers of women receiving valproate and children exposed to valproate during pregnancy.

[200] Veroniki, AA et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Medicine* 2017 **15**:95 https://doi.org/10.1186/s12916-017-0845-1

[201] Veroniki, AA et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open* 2017;**7:**e017248. doi:10.1136/bmjopen-2017-017248

[202] https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0#public-hearing-section. A summary was published shortly after: https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf

Oct 2017	Sanofi written evidence; PRAC	Sanofi participated in the PRAC Stakeholder group meeting where advice from SAG Psychiatry and the SAG Neurology was sought. The final PRAC assessment report[203] detailed the advice: • *For focal epilepsies, there are a number of alternatives to valproate with either superior or similar efficacy, and valproate should not be initiated as a first-line treatment.* • *Some patients who are drug resistant become seizure free with valproate and there are specific epileptic syndromes where valproate remains the most appropriate treatment. Complete contraindication in female patients may then hinder optimal treatment of some patients.* • *When valproate is initiated in women and girls with childbearing potential, the decision must be taken and treatment monitoring performed by a specialist. The need for valproate should be regularly re-evaluated.* • *Risks such as seizures, sudden death from epilepsy, replacement/withdrawal and teratogenicity should be considered. The SAG experts stated there could be a disadvantage to discontinue or switch valproate during pregnancy. Current guidelines state that valproate withdrawal should be undertaken gradually (over weeks to months), but there is no evidence that could be used to recommend a specific scheme for either switch or discontinuation of valproate.* • *A substitution early in life is recommended to reduce effects and disruption.* • *Valproate has some place in bipolar disorder, but not as a first-line treatment. The experts could not identify*
Oct 2017	Sanofi written evidence	Sanofi met with the Pharmacists Group of the EU ("PGEU") in Brussels to discuss the role of pharmacists in communicating safety information to patients.
Oct 2017	Hansard[204]	[19 Oct] Commons Debate on 'Valproate and Foetal Anticonvulsant Syndrome'. Norman Lamb "That this House notes: • a systematic failure to inform women of the dangers of taking the epilepsy drug sodium valproate during pregnancy;

[203] Published February 2018 - https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-assessment-report_en.pdf

[204] Hansard. 19 October 2017. Volume 629. Valproate and Foetal Anticonvulsant Syndrome. Debate in Commons Chamber. http://bit.ly/2EilvGw

		• welcomes the launch of the Valproate Toolkit by the MHRA, but notes with concern a recent survey which found that 68 per cent of women have still not received these safety warnings; • calls on the Government to take immediate steps to ensure that the materials in the Valproate Toolkit are distributed; • calls on the Government to require all clinicians to discuss annually with the patient, the risks during pregnancy before a prescription is renewed; • calls on the Government to bring forward proposals for a care plan and financial assistance to the victims of sodium valproate in pregnancy and their families." This was a wide-ranging discussion, in which the limitations of the valproate toolkit and women not being appropriately informed of the risks was emphasised. Other key points raised included: • Deliberate withholding of information from patients in the 1970s ("fruitless anxiety"), given the recent history of thalidomide • The need to investigate the history (e.g. whether the risk was downplayed by Sanofi) • Looking at other issues in which historical paternalistic attitudes play a key role (e.g. Primodos) • Specialist care provision to ensure appropriate women targeted • Failure of system to recognise a pattern and act - e.g. clear that during a period of time the drug is being prescribed significantly more than guidance suggests is appropriate, why did the regulator, drug company and Government not act? • Research needed on in-utero effects for women who have long-term health problems managed by medication Norman Lamb highlighted the following as steps that needed to be taken: 1) Toolkit should be mandatory, not voluntary 2) Annual discussion with GP or other health professional 3) Access to specialist units 4) Publish prescribing rates for valproate for every CCG 5) Ensure valproate is only taken by women of child-bearing potential when there is no other option 6) The Government's duty to provide a financial support package – "..they have the responsibility here and now to do right by these people. There is

		an overwhelming moral case for them to do that, and it is not good enough for Ministers to simply say that support is available locally through local authorities or CCGs. These families have suffered an injustice, and the Government have a moral obligation to address it." Mr Lamb gives the example of the French fund in support of this. 7) Statement of regret or apology 8) Inquiry or panel to understand how it has happened, how it could have gone on for so long, and what lessons can be learned to ensure it does not happen again. The Minister of State, Department of Health reflected on the positive changes away from a paternalistic attitude in medical practice. He highlighted the historical actions taken, and the actions of the MHRA in initiating the Europe-wide review and steps taken since, including improving awareness and tracking changes in prescribing. The motion was passed. Key issues from this debate were raised again on Oral Questions on the 19 Dec.
Nov 2017	MHRA/Sanofi written evidence	MHRA updated Sanofi on recommendations made by the CHM Expert Working Group on valproate, to contraindicate valproate in pregnant women and women of child bearing age not using an effective contraception in both bipolar disorder and epilepsy indications. MHRA requested that Sanofi should consider submitting an application for a variation to the UK valproate marketing authorisations to update the SmPCs in line with the EWG recommendations. Sanofi suggested that this should wait the outcome of the PRAC final recommendation which was expected shortly.
2018	Published article	*Barton et al*[205] - Prospective cohort study of 105 children. Exposure to valproate in utero was associated with lower scores on neuropsychological assessment of verbal and nonverbal memory, particularly in those exposed to higher doses. Exposure to carbamazepine was also associated with higher impairment on nonverbal memory measures.

[205] Barton et al. Memory Dysfunction in School-Aged Children Exposed Prenatally to Antiepileptic Drugs. Neuropsychology 2018; 32(7):784-796

		The authors note that this study was designed to address methodological shortcomings of previous studies (e.g. the study was prospective, participants were recruited from a pregnancy register, few mothers declined to participate, and confounding factors were controlled for). However they did not use an unexposed control group. They call for future studies with larger samples in order to investigate the effects of VPA monotherapy compared to VPA polytherapy.
Jan 2018	BBC	BBC Inside Out programmes on sodium valproate.[206]
Feb 2018	PRAC	PRAC Press Release issued[207] which stated concerns that previous measures had not been sufficiently effective, and detailed the following measures recommended to avoid valproate exposure in pregnancy: • For migraine or bipolar disorder – valproate should not be used in pregnancy, and female patients must be on the PPP • For epilepsy – valproate must not be used unless conditions of the PPP have been met and should not be used in pregnancy; however some women who are resistant to other treatment may have to continue treatment during pregnancy with specialist support. • Outer packaging of valproate medicines must include a visual warning, and patient reminder card will be attached for pharmacists to discuss with patients each time the medicine is dispensed • Companies that market valproate should provide updated educational materials for healthcare professionals and patients • Companies marketing these medicines should carry out additional studies to further characterise these risks and to monitor ongoing valproate use It also outlined the key elements of the PPP: • Counselling patients about the risks of valproate treatment and explaining the need for effective contraception • Supporting patients to make informed decisions about their treatment • Pregnancy tests before starting and during treatment as needed • Treatment reviews at least annually, including a new risk acknowledgement form

[206] Inside Out London https://www.bbc.co.uk/programmes/b09p2d81; and Inside Out World https://www.bbc.co.uk/programmes/n3ct3syk

[207] https://www.ema.europa.eu/en/documents/press-release/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf

21st Feb 2018	Hansard	House of Commons - The Secretary of State for Health and Social Care announced an Independent Medicines and Medical Devices Safety Review (IMMDS Review). One of the interventions the Review was tasked with considering was the use of valproate in girls and women of childbearing potential.[208]
Feb 2018	Sanofi/MHRA	Sanofi met with MHRA to consider how the recommendations of the PRAC and the new risk minimisation measures could be implemented in the UK as quickly as possible. Sanofi provided an update on progress on packaging changes, dispensing labels as an interim measure, and educational materials. Sanofi were also asked to consider and make proposals to the MHRA for a pregnancy registry.
Mar 2018	MHRA written evidence	Sodium valproate expert working group minutes[209] noted that a number of points made on wording of the SmPC and PIL at the previous meeting were not fully reflected in the final versions. The MHRA informed the group that drafting of the changes at EU level necessarily meant that there was compromise on some aspects of the wording in the final regulatory documents; however the wording of the educational materials was for national agreement and therefore these could be amended to ensure clarity as long as they remained consistent with the regulatory position.
Mar – Jun 2018	Sanofi written evidence	Sanofi commenced submission of educational materials as recommended by the PRAC, to MHRA for review and approval. This included: • Dear Healthcare Professionals Communication ("DHPC") and HCP guide • Patient guide and card • Warning label for pharmacy 'white boxes' • Annual Acknowledgement of Risk Form • Pharmacy Poster
Mar 2018	Sanofi	Sanofi UK submitted applications for variations to the valproate marketing authorisations to implement the outcome of the Article 31 referral in the UK SmPCs (prior to the CMDh final decision). Final approval was received in May 2018.

[208] Hansard. 21 February 2018. Volume 636. Commons Chamber. Medicines and Medical Devices Safety Review. http://bit.ly/2KtutqA

[209] MHRA written evidence. Annex Q. Commission on Human Medicines. Sodium Valproate Expert Working Group. Minutes of meeting held on Thursday 29 March 2018

	Published evidence	*Paton et al*.[210] – Clinical audit of prescribing practice across 55 Mental Health Trusts in found that 24% of women diagnosed with bipolar disorder aged younger than 50 years were prescribed valproate-containing medicines: in only half of such women was there documented evidence that information had been provided on the risks for the unborn child and the need for adequate contraception.
Apr 2018	NICE written evidence	NICE Guidelines were updated in line with the recommendations of the PRAC.[211] A number of interim updates were available on the website in line with updates to the MHRA guidance. These have continued to be updated.[212]
Apr 2018	Sanofi written evidence	Sanofi submitted applications to add the pregnancy pictogram to the primary packaging of all valproate products (blister). This change was approved on 2 May 2018, to be implemented into production within 6 months of approval.
Apr 2018	Sanofi written evidence	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 24 January 2015 - 23 January 2018. This was a routine submission in respect of the Epilim marketing authorisations.
Apr 2018	MHRA	The MHRA released Drug Safety Update 'Valproate medicines: contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met'.[213] This stated that valproate medicines must no longer be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place. Health Care Professionals should ensure all women and girls (and their parent, caregiver, or responsible person, if necessary) are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy. On the same day an alert was released, emphasising the PPP. It also stated "Despite repeated communications on this risk, it is estimated that 400 women in the UK took valproate medicines during pregnancy in 2016."[214]

[210] Paton, C et al. A UK clinical audit addressing the quality of prescribing of sodium valproate for bipolar disorder in women of childbearing age. BMJ Open 2018;8:e020450. doi:10.1136/ bmjopen-2017-020450
[211] NICE Guideline: The epilepsies - The diagnosis and management of the epilepsies in adults and children in primary and secondary care 2004 (Updated 2018) (CG20)
[212] See https://www.nice.org.uk/guidance/cg137/chapter/Update-information
[213] https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met
[214] Central Alerting System (CAS). CMO Messaging. Valproate contraindicated in women of childbearing potential unless there is a Pregnancy Prevention Programme. 24 April 2018. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102736

May 2018	Sanofi	Sanofi submitted an application for a variation to the existing marketing authorisations to add a 30s pack size to Epilim and Depakote packs where 30s were not currently registered. This was approved on 14 May 2018. Artwork for cartons was submitted on 30 May 2018 and approved on 8 June 2018.
May – Dec 2018	MHRA written evidence	Throughout 2018 the MHRA published a number of Drug Safety Updates providing information about the PPP materials,[215] actions required from GPs, specialists and dispensers,[216] and later in the year, warning practitioners that there was currently patchy compliance with the PPP.[217]
31 May 2018	EMA	The European Commission adopted a final decision following the Article 31 referral, confirming the recommendations of the PRAC in an EU-wide legally binding decision.[218]
June 2018	ANSM (France)	ANSM publish a cohort study[219] based on national data estimating risk of neurodevelopmental disorders in children exposed to valproate in utero. The results highlight a marked dose-dependent risk of early neurodevelopmental disorders linked with exposure to valproic acid indicated in epilepsy during pregnancy. Evidence that the second and third trimester are particularly significant in terms of exposure to valproate and development of these neurodevelopmental defects.
July 2018	ANSM (France)	Letter sent to doctors, explaining that in epilepsy, valproate is contraindicated during pregnancy (unless no appropriate therapeutic alternative) and in women of childbearing age (unless other treatments prove ineffective or are not tolerated and if all conditions of the PPP are not met).
July 2018	Sanofi written evidence	Packs of PPP materials and DHPC sent to pharmacists, specialists, GPs and other healthcare professionals.

[215] 24 May 2018 https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-pregnancy-prevention-programme-materials-online;
[216] 25 September 2018 https://www.gov.uk/drug-safety-update/valproate-pregnancy-prevention-programme-actions-required-now-from-gps-specialists-and-dispensers. This included a video which can be found here: https://youtu.be/VuBq2M1Me04
[217] 18 Dec 2018 https://www.gov.uk/drug-safety-update/valproate-medicines-are-you-in-acting-in-compliance-with-the-pregnancy-prevention-measures
[218] https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-new-measures-avoid-valproate-exposure-pregnancy-endorsed_en-0.pdf
[219] ANSM, Risque de troubles neuro-développementaux précoces (avant l'âge de 6 ans) associé à l'exposition in utero à l'acide valproïque et aux autres traitements de l'épilepsie en France - Etude de cohorte à partir des données du SNDS. 2018.

Aug 2018	Ireland	Health Service Executive (HSE) Ireland published *'Rapid assessment of the number of women and children exposed to sodium valproate in Ireland 1975-2015'.*[220] This aimed to provide an estimate of the likely prevalence of major congenital abnormalities and neurodevelopment disorders arising from exposure to sodium valproate in the womb, between 1975 and 2015. The report clearly sets out the limitations to its approach (no single data source; data sources could not be linked; not possible to take into account factors such as duration, dosage or mono- or poly-therapy; socio-economic differences; includes prescribing for epilepsy and bipolar disorder, but not off-licence, e.g. for migraine). It emphasises that the figures produced should therefore only be viewed as broad guide. It estimates that between 1975 and 2015 inclusive: • approximately 3,083 maternities were in women who were taking valproate when becoming pregnant; • approximately 3,126 babies were potentially exposed to valproate in utero • on the basis of emerging international data regarding rates of major congenital malformation and neurodevelopmental delay, **between 153 and 341 children will have experienced a major congenital malformation and up to 1,250 children will have experienced some form of neurodevelopmental delay.**
Sept 2018	MHRA	MHRA wrote to the General Pharmaceutical Council, the General Medical Council and the Care Quality Commission about evidence of a lack of compliance with the PPP.
Sept 2018	MHRA	MHRA wrote to NICE asking them to take forward the work on development of a cross-disciplinary valproate guideline.
Oct 2018	MHRA	Letter sent to pharmacists via CAS[221] from MHRA and four Chief Pharmaceutical Officers emphasising that all dispensed medicines containing valproate should be accompanied by a statutory patient information leaflet.
Oct 2018	Published article	*Heneghan and Aronson* [222]- This paper builds on the work of Tanoshima et al, which uses meta-analysis to assess when a doubling of risk of congenital malformations can be shown from existing data. • 1990 – cumulative risk ratio reaches statistical significance • 2004 – cumulative risk ratio shows double the risk

[220] This can be downloaded from the Epilepsy Ireland webpage
[221] https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102805
[222] Heneghan, C and Aronson, JK (2018) Sodium valproate: who knew what and when? Cumulative meta-analysis gives extra insights. BMJ Evidence-Based Medicine 2019;24:127-129. (Online October 2018)

		• 2014 – latest estimate in more than 20,000 individuals confirms the risk is more than doubled
Nov 2018	Published article	*Yunos and Green* [223] - Retrospective study of 29 cases of FVS diagnosed between 1995 and 2016. The study concludes that FVS is still seen in the Irish population despite that teratogenicity of valproate being known for over 32 years, and that it is very important to create public and professional awareness to prevent FVS whenever possible.
Dec 2018	RCPsych	Position statement published on '*Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness*'.[224] This statement discusses: the recent regulatory guidance; the efficacy and alternatives of use of valproate-containing medicines in psychiatric practice; and advice for switching patients to alternative medicines. It advises that most women of childbearing potential who are undergoing psychiatric care should be withdrawn from continued treatment with valproate-containing medicines. Those who wish to continue must be on an effective PPP. Women who become pregnant whilst on valproate must be referred to an appropriate specialist for review.
Jan 2019	Published article	*Christensen et al*[225] - Population-based cohort study in Denmark. Maternal use of valproate (but not other AEDs) was associated with an increased risk of ADHD in the offspring.
March 2019	Hansard [226]	[21 March] Debate on 'Valproate Pregnancy Prevention Programme'. This focussed on raising awareness of non-compliance with the PPP and the monitoring and action that is taking place to correct this. 'Estimates of the number of children still being affected by this drug vary. In February 2016, the right hon. Member for North Norfolk (Norman Lamb), the then Minister for Life Sciences, stated that 336 children are exposed to valproate every year. Figures from the Clinical Practice Research Datalink suggest that the figure could in fact be 176. However, even the lower number would imply that 7,000 children have been harmed by valproate since it first came on the market in 1973, with a further 28 a month still exposed to it.'

[223] Mohd Yunos, H & Green, A. Fetal valproate syndrome: the Irish experience. Irish Journal of Medical Science 2018; 187: 965. doi: 10.1007/s11845-018-1757-6
[224] https://www.bap.org.uk/pdfs/PS04-18-December2018.pdf
[225] Christensen et al. (2019) Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA Network Open. 2019;2(1):e186606. doi:10.1001/jamanetworkopen.2018.6606
[226] Hansard. 21 March 2019. Volume 656. Valproate Pregnancy Prevention Programme. Debate in Commons Chamber. http://bit.ly/2Jym1pH

March 2019	Royal Colleges	'*Guidance Document on Valproate Use in Women and Girls of Childbearing Years*'[227] published by RCOG, ABN and RCP, and endorsed by a number of professional organisations. The document sets out the new regulations and provides practical information and guidance for clinicians who may prescribe valproate to girls and women of childbearing potential for epilepsy or psychiatric treatment for. This includes guidance for complex situations arising in practice, and special situations such as status epilepticus.
March 2019	New Zealand	New Zealand 'Medsafe' - Alert Communication – warning of risk of birth defects and developmental problems. Indication for use in bipolar disorder was changed. Sodium valproate only to be used in women of childbearing potential when all other treatments are ineffective or not tolerated. Women must use effective contraception while taking sodium valproate.
April 2019	RCPCH and BPNA	Published guidelines on 'Prescribing valproate to female patients under 18 years of age'[228]. These guidelines set out the approach to prescribing valproate might be expected to vary in female patients in the following age groups: under 10 years; 10 – 12; 13 – 15; and 16 – 18.
April 2019	ANSM (France)	ANSM published a report '*Anti-epileptics during pregnancy: Current State of knowledge on the risk of malformations and neurodevelopment disorders*'. This includes figures clearly summarising these risks – valproate has the highest risk of frequency of malformations and is currently the only AED to be identified as a confirmed risk for neurodevelopmental disorders.
July 2019	Published article	*Clayton-Smith et al* [229] - A consensus document on the diagnosis and management of Fetal Valproate Spectrum Disorder, produced by the European Reference Network for Congenital Malformations and Intellectual Disability. The paper outlines: • Comment on measures to avoid valproate exposure in pregnancy and care and advice during the preconception period and pregnancy • Diagnostic criteria for FVSD • Recommendations of management of FVSD, covering preconception management to adults with FVSD and specific aspects of clinical management.

[227] https://www.rcog.org.uk/globalassets/documents/guidelines/valproate-guidance-march-2019.pdf
[228] https://www.rcpch.ac.uk/sites/default/files/2019-04/bpna_rcpch_valproate_guidance_130419_0.pdf
[229] Clayton-Smith, J et al. Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability. Orphanet Journal of Rare Diseases 2019; 14: 180

		It notes that in the future, it may be possible to produce variations of the care plan with the same core recommendations, but include country or healthcare system specific information. The authors reflect on the reasons for the delay in recognising the teratogenic effects of valproate exposure in utero, and the resource implications of the recommendations. The group have also produced one-page summary sheets targeted specifically for parents, the paediatric team, general practitioners who will be overseeing adult care and teachers.
Aug 2019	Published article	Tomson et al [230] - the authors analysed data from the EURAP registry to compare changes in prescribing patterns of antiepileptic drugs in pregnant women with epilepsy and prevalence of major congenital malformations in their children. Three time periods were considered: 2000-2005, 2006-2009, and 2010-2013. Over time, use of valproic acid and carbamazepine decreased, and lamotrigine and levetiracetam increased. The prevalence of major congenital malformations with monotherapy exposure decreased from 6% in 2000-2005 to 4.4% in 2010-2013. The authors' analysis suggests "that changes in prescription patterns played a major role in the reduction of teratogenic events."
Sept 2019	Published article	Owens[231] – In this editorial, Professor Owens[232] discusses the use of sodium valproate in psychiatry. He argues that valproate/valproic acid is overused in psychiatry, and that the profession must '*change its perception of valproate, concentrating less on how 'easy' its use appears to be and focusing more on its diverse and poorly understood 'risks'.'* He acknowledges that valproate may be useful in a small number of patients with bipolar disorder, but considers current prescribing patterns to be unjustified.

[230]Tomson, T et al. for The EURAP Study Group. Declining malformation rates with changed antiepileptic drug prescribing: An observational study. Neurology Aug 2019, 93 (9) e831-e840; doi: 10.1212/WNL.0000000000008001

[231] Owens, D. Sodium valproate in psychiatric practice: Time for a change in perception. British Journal of Psychiatry Sept 2019, 215(3), 516-518. doi:10.1192/bjp.2019.137

[232] Professor Owens is psychiatric commissioner on the Commission on Human Medicines and a member of the European Medicines Agency's Scientific Advisory Group on Psychiatry. He chaired the European Medicines Agency's review of the psychiatric use of valproate in pregnancy and women of childbearing potential.

Key to Abbreviations

ABN	Association of British Neurologists
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse Drug Reaction
AED	Antiepileptic Drug
ANSM	Agence Nationale de Sécurité du medicament et des produits de santé
APPG	All Party Parliamentary Group
ASD	Autism Spectrum Disorders
BMA	British Medical Association
BPNA	British Paediatric Neurology Association
CAS	Central Alerting System
CDC	Centers for Disease Control and Prevention, USA
CHM	Commission on Human Medicines
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CRM	Committee on Review of Medicines (est. 1975)
CSI	Company core safety information
CSM	Committee on Safety of Medicines
CSM/AR	Committee on Safety of Medicines, Adverse Reactions Sub-committee
DHPC	Dear Healthcare Professional Communication
DHSS	Department of Health and Social Security
DUS	Drug Utilisation Study
EC	European Commission
EMA	European Medicines Agency
EURAP	European Registry of Antiepileptic drugs and Pregnancy
EWG	Expert Working Group
FACS	Fetal Anti-Convulsant Syndrome
FDA	Food and Drug Administration, USA
HCP	Healthcare Professional
HSCIC	Health & Social Care Information Centre (now NHS Digital)
IGAS	Inspection Générale des Affaires Sociales (France)
MCA	Medicines Control Agency
MHRA	Medicines and Healthcare products Regulatory Agency
NTD	Neural Tube Defect
PIL	Patient information leaflet
PPP	Pregnancy Prevention Plan
PRAC	Pharmacovigilance Risk Assessment Committee (EU)
PSUR	Periodic Safety Update Report
QOF	Quality and Outcomes Framework
R&C	Reckitt and Colman
RCP	Royal College of Physicians
RCOG	Royal College of Obstetricians and Gynaecologists
RCPCH	Royal College of Paediatrics and Child Health
RCPsych	Royal College of Psychiatrists
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration, Australia

1. *BN 116/17 CSM/AR/1/73 Committee on Safety of Medicines. Sub-Committee on Adverse Reactions. Meetings 17.1.1973-21.11.1973.* .
2. M. Commission, MHRA supplementary evidence. Medicines Commission MC 76/112A 'A Note on Epilim – Sodium Valproate'. (1976).
3. <2000-02-28 OQ (Lords) Epilepsy - Hansard.pdf>.
4. <2002-05-23 DEBATE (Lords) Epilepsy - Hansard.pdf>.
5. <2010-10-12 DEBATE Epilepsy Services - Hansard.pdf>.
6. *On the State of the Public Health: The Annual Report of the Chief Medical Officer of the Department of Health 2001* (2001 https://webarchive.nationalarchives.gov.uk/20130105045609/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4082273.pdf).
7. DH, Improving Services for People with Epilepsy: Department of Health Action Plan in response to the National Clinical Audit of Epilepsy-Related Death. (2003).