**Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B vaccine) and**

**Sudden Death – a review of the regulatory evidence from the European Medicines Agency**

**Jacob Puliyel** MD MRCP MPhil

Head of Department of Pediatrics

St Stephens Hospital

Delhi 110054

[puliyel@gmail.com](mailto:puliyel@gmail.com)

**C Sathyamala** MBBS, MSc (Epidemiology), PhD (Development Studies)

Independent Researcher

121, Pocket-B, SFS Flats, Sukhdev Vihar

New Delhi 110025

csathyamala@gmail.com

Key words

Sudden infant death, Sudden unexpected deaths, Periodic Safety Update Reports

Address for correspondence

Jacob Puliyel

Head of Department of Pediatrics

St Stephens Hospital

Delhi 110054

Phone 9868035091

puliyel@gmail.com

**Abstract**

There have been a number of spontaneous reports of sudden deaths soon after administration of Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B vaccine).

The manufacturer GlaxoSmithKline (GSK) continuously provides the European Medicines Agency (EMA) confidential periodic safety update reports (PSUR) about Infanrix hexa. The latest is the 19th PSUR. Each PSUR contains an observed/expected analysis of sudden deaths, which show that the observed deaths soon after immunization, are lower than that expected by chance.

We analyzed the data provided in the PSUR. It is apparent that the deaths that were acknowledged in the 16th PSUR were deleted in the 19th PSUR. Including these deaths, the rate of observed deaths soon after vaccination in the children older than one year were significantly higher than would be expected by chance.

The manufacturer must explain the faulty figures that they submitted to the regulatory authorities. The procedure undertaken by the EMA to evaluate the manufacturer’s claims in the PSUR need to be reviewed.

The Drug Controller General of India nearly automatically accepts drugs and vaccines approved by the EMA . The reliance on due diligence by the EMA need to be evaluated.

**Introduction**

Two hexavalent vaccines Infanrix Hexa® (GlaxoSmithKline plc - GSK) and Hexavac® (Sanofi Pasteur MSD, SNC), which combine diphtheria, tetanus, acellular pertusis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B were authorized to be marketed in the European Union on 23 October 2000. Following authorization there were a number of spontaneous reports of sudden unexpected deaths soon after administration of the vaccine. In 2005, von Kries and colleagues (1) performed the first detailed analysis in which the observed deaths soon after vaccination were compared with the deaths expected by chance. They found a significantly increased standardized mortality ratio (SMR) within two days after vaccination of Hexavac® in children vaccinated in the 2nd year of life. The same was not seen with Infanrix hexa. After the withdrawal of Hexavac in 2005 at the request of the marketing authorisation holder, Infanrix Hexa continued to be marketed in Europe (2).

According to European law, the European Medicines Agency (EMA) is accountable for the protection of public health through evaluation of the medicines it approves as the regulatory authority. The manufacturers are responsible for the efficacy, quality and safety of their drugs (3).

In \_, the Italian Court of Justice, Nicola Di Leo, made GlaxoSmithKline’s confidential 15th and 16th Periodic Safety Update Reports (PSURs, from 2009 to 2011) available to the public by (4). to write a report to the European Parliament.

Our commentary is based on the 19th PSUR (incorporating PSUR 17, 18 and 19, from 15 January 2015, provided to us by Dr Bolgan) and reviews sudden deaths following the use of Infanrix Hexa. The PSUR’s and the manufacturer responses are available to readers on request…?.

**PSUR 15 – Clustering of Deaths after Vaccination with** Infanrix Hexa

Most deaths occurring in the neonatal period are mainly due to infections, congenital defects, malignancies and accidents. Seldomly do infants die without any evident cause and such deaths are classified as SIDS (Sudden Infant Death Syndrome) or SUD (Sudden Unexpected Deaths). A number of vaccines are administered to children under the age of 2 years and some SIDS/SUD occur associated with vaccination. To ascertain if SIDS/SUD are caused by vaccination an observed/expected analysis of sudden deaths (SD) is performed to estimate if the deaths observed after vaccination exceeds that which can be expected by chance.

**Sudden Deaths: Observed vs. Expected**

“Given the attention that has been given to the occurrence of sudden deaths in children in the second year of life within 14 days of the administration of hexavalent vaccines, the Company evaluated whether the number of sudden deaths reported in this age group exceeded the number one could expect to occur by coincidence.

Since the distribution of the age at which subjects are vaccinated is unknown, the Company assumed that the proportion of adverse events by age is representative for the actual age distribution at vaccination. It can thus be estimated that 90.6% of all recipients of Infanrix hexa™ were in their first year of life, and 9.4% were in their second year of life. Therefore the number of doses (since launch) was estimated to be 54,927,729 and 5,698,904 respectively. Given that Germany is the main country where Infanrix hexa™ doses are distributed (close to 30% only in Germany); It was assumed that the incidence of sudden death observed in Germany is representative for the entire population of Infanrix hexa™ recipients (German Federal Bureau of Statistics, Statistisches Bundesamt; incidence rate in 1st year of life: 0.454/1,000 live births; second year: 0.062/1,000 live births, data 2008). A healthy vaccinee correction factor (taken here to be 0.8 based on various case-control studies of SIDS or SUID) was applied.”

The PSUR’s document the deaths that have happened within 20 days of vaccination. They then consider it against the expected deaths during the same period.

**Table 1**

**Observed/Expected Analysis of Sudden Deaths in PSUR 15**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Time since Vaccination  (days) | Observed  (1st year) | Expected | Observed (2nd  year) | Expected |
| Less than 1 day | 10 | 54.7 | 1 | 1.98 |
| 1 day | 20 | 109.3 | 2 | 3.96 |
| 2 days | 33 | 164 | 3 | 5.94 |
| 3 days | 42 | 218.6 | 3 | 7.92 |
| 4 days | 49 | 273.3 | 3 | 9.9 |
| 5 days | 50 | 327.9 | 3 | 11.88 |
| 6 days | 50 | 382.6 | 3 | 13.86 |
| 7 days | 51 | 437.3 | 4 | 15.84 |
| 8 days | 52 | 491.9 | 5 | 17.82 |
| 9 days | 54 | 546.6 | 5 | 19.8 |
| 13 days | 54 | 765.2 | 6 | 27.72 |
| 15 days | 55 | 874.5 | 6 | 31.68 |
| 16 days | 56 | 929.2 | 6 | 33.66 |
| 18 days | 57 | 1038.5 | 6 | 37.62 |
| 19 days | 58 | 1093.1 | 6 | 39.6 |

(Source: Table 24 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance report to Regulatory Authority PSUR 15)

The observed deaths were less than that was expected (Table 1). However, among the infants, there was a clustering of deaths immediately following vaccination, with 42 deaths taking place in the first three days after vaccination, and only 8 deaths in the next 3 days. 93% of deaths (54 deaths) in the infants below 1 year, occur in the first 10 days and 7% (2 deaths) occur in the next 10 days. Had the deaths been ‘coincidental SIDS deaths’ this disparity in number of deaths in the two time periods, would not have been observed. The fact that rate of deaths decreases rapidly as time elapses after immunization suggests that the deaths could be related to vaccination. These are otherwise ‘unexplained deaths’ and will have been investigated by a competent forensic team and the immunization records will have been examined to check if the infant was up to date with its vaccinations. Reporting bias has little role under these circumstances.

In the same way, in children older than one year, 83.3% deaths (5 deaths) occur in the first 10 days and 17% (1 death) occurs in the next 10 days. I have previously commented on the fact that the sudden deaths are clustered around the date of vaccination, which is also seen in the 16th PSUR (6).

**GSK Response**

The CEO of GlaxoSmithKline, Sir Andrew Witty, responded to this criticism (7). He wrote that,

“Based on the figures presented in Table 36 of the GSK PSUR (*PSUR 16- explanatory note added by me)* referred to above and a second table that you prepared entitled “Daily increment in Sudden Death following Infanrix hexa in children in their first and second year of life,” you have suggested that if the reported sudden death rates had been “coincidental SIDS deaths,” there should not have been a difference in the number of reported sudden deaths between the two periods of time (0-9 days v. 10-19 days). Such an assumption (that there should be no difference in the number of cases reported during the two time periods) could be valid only if the reporting of sudden death cases were to occur independently of the time from vaccination to death. In other words, the underlying premise of your analysis would thus be valid only if a sudden death case were to have equal probability of being spontaneously reported regardless of whether it occurred on the day of vaccination or 2 weeks later.  
  
Such an equal probability is highly unlikely. We know from the extensive spontaneous report data available to us that reporting of cases does not occur independently of the time from vaccination to event. On the contrary, available data show that potential reporters are much more likely to think about a potential causal association and thus report an event when the event occurs shortly after vaccination than when it occurs weeks later.   
  
In light of the above, we remain confident in the conclusions previously reached by GSK and shared with regulatory agencies and public health authorities worldwide that the currently available data do not suggest an increased risk of Sudden Infant Death following vaccination with Infanrix-hexa. Nevertheless, as part of our ongoing monitoring and evaluation of the safety of all of medicines and vaccines, we will continue to monitor and evaluate all cases of Sudden Infant Death reported and share the results of those analyses with authorities in those countries where Infanrix hexa is licensed. Should the available data and information change to suggest that there is such an increased risk, we remain committed to promptly notifying the authorities and to taking the necessary actions to communicate such data and information to healthcare professionals.”

This argument was not taken forward at that time, given this plausible explanation by the CEO of GSK that persons reporting SD are much more likely to think about a potential causal association and thus report an event to GSK when the event occurs shortly after vaccination than when it occurs weeks later and given the assurance that GSK will continue to monitor and evaluate all cases of Sudden Infant Death reported and “should the available data and information change to suggest that there is such an increased risk, we remain committed to promptly notifying the authorities and to taking the necessary actions to communicate such data and information to healthcare professionals.”

It was noted at the same time that the response included a tacit admission of the fact that only deaths reported to GSK are included in the ‘observed deaths’ analysis and this is likely to be a gross underestimation of deaths in the post vaccination period.

**PSUR 16 –Doubling of Expected Deaths**

The number of deaths in the 2nd year in the 16th PSUR was higher than expected in the first 5 days after vaccination. Presumably to match the observed deaths, expected deaths in the second year was doubled. This was accomplished by assuming that 20% of all doses were used in the second year (in the 16th PSUR) instead of 9% as reported in the 15th PSUR (Table 36 on page 249).

“It can thus be estimated that 75% of all recipients of Infanrix hexa were in their first year of life, and 20% were in their second year of life (5% were not attributable because the age at vaccination was unknown). Therefore the number of doses (since launch) was estimated to be 54,7 and 14,6 millions respectively.”

If all children who received the first dose of the vaccine went on to receive four doses and the last dose was in the second year of life, then it can be estimated that one fourth (25%) of the doses were used in children over the age of one year. This is the vaccine-schedule recommended in Germany. However not all children receive all the doses recommended. Furthermore, some countries advise three doses in the first year and no doses in the second year. In the 15th PSUR it was estimated that 91% doses were used in infants under one year and 9% of the doses were used after the age of one year. The 16th PSUR estimate of doses received in the second year was more than doubled from 9.4% to 20% and so the estimate of expected deaths was doubled.

**Table 2**

**PSUR 16: Observed/Expected death in 2nd year**

|  |  |  |  |
| --- | --- | --- | --- |
| Time since  Vaccination  (days) | Observed  (2nd year)  PSUR 16 | Expected death reported in 16 PSUR after  doubling  recipient numbers  (20% doses in 2nd year) | Expected deaths  if 9.4% children  vaccinated were in  their second  year of life  ( as in the 15th  PSUR)\* |
| 0 | 2 | 1.98 | 0.93 |
| 1 | 5 | 3.96 | 1.86 |
| 2 | 6 | 5.94 | 2.79 |
| 3 | 6 | 7.92 | 3.72 |
| 4 | 6 | 9.9 | 4.65 |
| 5 | 7 | 11.88 | 5.58 |
| 6 | 7 | 13.86 | 6.51 |
| 7 | 7 | 15.84 | 7.44 |

Source - Adapted from (Table 36 on page 249)

\*Calculated by the author

Observed deaths exceeded expected deaths in the first 3 days even after doubling the expected deaths. It was higher than expected deaths for the first 7 days, if it was assumed that 9.4% doses were used in the second year.

**PSUR 19: Expected Deaths Weighted by Country and Yearly Proportion of Doses**

In PSUR 19, a weighted average of sudden deaths by calendar time of the German, French and Dutch incidence rate was calculated to arrive at the expected incidence of sudden deaths. This was calculated as 0.0102/1000 live births for the second year. This figure is one sixth of the expected rate used in PSUR 15 and 16 which calculated expected sudden deaths at 0.062/1000 live births using German data.

The Poisson 95%CI of the observed deaths in the second year is reported in Table 8 on Page 447 of the 19th PSUR. It is reported that for the second year of life the observed SDs was higher than expected within a risk period 1 to 4 days post vaccination, though not significantly.

**Missing Deaths in the 19th PSUR**

The total doses of the vaccine went up from 69 million in PSUR 16 to 112 million doses in the PSUR 19 where 20% of doses distributed were presumed to have been given to children in the second year of life (Page 436 to 448).

The sudden deaths reported in the PSUR 16 are missing from the PSUR 19 and cumulative deaths reported are lower in the 19th PSUR than in the 16th PSUR. There are 5 deaths in the 20 days after vaccination in children over one year, reported in the 19th PSUR when 23 million doses were assumed to be administered. Up to 16 December 2011 – (the period of the 16th PSUR) 8 deaths had already been recorded for 15 million doses. This can happen if there were no additional deaths when 8.2 million extra doses were administered in the period between PSUR 16 and PSUR 19, and 3 of the children reported as dead earlier, are somehow alive now! All the 8 deaths reported in the PSUR 16 were in children in the second year and within 14 days of vaccination. We wonder why the three deaths were erased.

Table 3 presents the observed and expected deaths of the 19th PSUR after restoring the deaths reported in PSUR 16. (The figures for deaths, as reported in the 19th report are put in parenthesis, i.e. “[…]” )

**Table 3 Observed and Expected deaths in the second year 19th PSUR**

|  |  |  |
| --- | --- | --- |
| Time since Vaccination (days) | Assuming observed deaths in PSUR 19 must be at least the observed deaths in PSUR 16\* (Poisson 95%CI of actual observed deaths)  [Figure in brackets are the observed figure reported in 19th report after deleting 3 deaths] | Expected deaths according to 19 PSUR |
| 0 | 2 (0.24-7.22) [0] | 0.54 |
| 1 | 5 (1.62-11.67) [2] | 1.08 |
| 2 | 6 (2.20-13.05) [3] | 1.62 |
| 3 | 6 (2.20-13.05) [3] | 2.16 |
| 4 | 6 (2.20-13.05) [3] | 2.70 |
| 5 | 7 (2.81-14.42) [3] | 3.24 |
| 6 | 7 (2.81-14.42) [3] | 3.77 |
| 7 | 7 (2.81-14.42) [3] | 4.31 |
| 8 | 7 (2.81-14.42) [4] | 4.85 |
| 9 | 7 (2.81-14.42) [4] | 5.39 |
| 10 | 7 (2.81-14.42) [4] | 5.93 |
| 11 | 7 (2.81-14.42) [4] | 6.47 |
| 12 | 7 (2.81-14.42) [4] | 7.01 |
| 13 | 8 (3.45-15.76) [5] | 7.55 |
| 14 | 8 (3.45-15.76) [5] | 8.09 |
| 15 | 8 (3.45-15.76) [5] | 8.63 |
| 16 | 8 (3.45-15.76) [5] | 9.17 |
| 17 | 8 (3.45-15.76) [5] | 9.71 |
| 18 | 8 (3.45-15.76) [5] | 10.24 |
| 19 | 8 (3.45-15.76) [5] | 10.78 |

Source: Data from Table 8 PSUR 19

(\*Data on deaths from the 16th PSUR from Table 36 on page 249)

When the observed death figures from the 16th PSUR are used, observed deaths are significantly higher than expected for the first four days after vaccination.

This may be why deaths reported earlier have been deleted from the 19th PSUR. The real purpose of the expected to observed analysis does not seem to evaluate whether number of sudden deaths after vaccination exceeded that expected to occur by chance, but in order to make it appear that the deaths with vaccine were unrelated events.

**Rationale to Assume 20.2% Doses are Used in the Second Year**

In the PSUR 19, it is assumed that 20.2% doses have been used in the second year:

“Since the distribution of the age at which subjects are vaccinated is not directly available, it was assumed that the frequency distribution of the age at onset of the first event in spontaneous cases reported is representative of the actual age distribution at vaccination. The age distribution from all (ie sudden death and non-fatal) spontaneous cases in the database with known age at event onset for Infanrix hexa was used to approximate the age distribution: 73.2% doses if Infanrix hexa were administered in the first year while 20.2% of doses were administered in the second year of life. “

It is futile to estimate the number of doses used in the second year from the ‘observed deaths’, and then use this ‘estimate of doses’ to calculate the ‘expected deaths’, and then to compare this ‘expected deaths’ with ‘observed deaths’ – given that the expected deaths is derived ‘estimate of doses’ derived from observed deaths in the first place.

Assuming that all deaths following vaccination are SIDS/SUD, and given that sudden deaths in the first year are 44 times more frequent than in the second year (0.454/1000 in the first year and 0.0102/1000 in the second year), 44 times as many children have to be vaccinated in the second year to reach the same number of deaths as in the first year. In a cohort of 100 deaths, if 20.3% of sudden deaths happen in the second year then 893 children have to be vaccinated in the second year for every 80 (approximation) vaccinated in the first year. In that case it must be assumed that 91% of all doses of Infanrix hexa are used in the second year and only 9% is used in the first year. This is the absurdity that one must conclude if we calculate dose distribution by age, from the age distribution of sudden deaths as done in the GSK document. The EMA seems to have accepted this unquestioningly.

The only way to estimate the number of doses used in the second year, is to look at the vaccination schedules in different countries and the dropout rate (children dropping out of the vaccination programme after receiving the first dose). By this estimation it would seem that 9.4% as employed in the 15 PSUR is probably a reasonable estimate of doses in the second year.

**Table 4. PSUR 16 Revised Observed/Expected death in 2nd year weighted by country, by yearly proportion of doses (as in PSUR 19).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time since  Vaccination  (days) | Observed  (2nd year)  PSUR 16  (Poisson  95%CI) | Expected  death  reported in  16 PSUR  (20% of doses  used over 1  year  (**Incidence SD**  Germany  **0.062/1000**) | Expected  death  reported in  16 PSUR  (9.4% of  doses used  over 1 year  (**Incidence SD**  Germany  **0.062/1000**) | **Incidence** SD weighted  by country by  yearly  proportion of  doses is  **0.0102/1000**  (9.4% of  doses used  over 1 year) | **Incidence** SD weighted  by country by  yearly  proportion of  doses is  **0.0102/1000**  (20% of  doses used  over 1 year) |
| 0 | 2 (0.24-7.22) | 1.98 | 0.93 | 0.15 | 0.32 |
| 1 | 5 (1.62-11.67) | 3.96 | 1.86 | 0.31 | 0.66 |
| 2 | 6 (2.20-13.05) | 5.94 | 2.79 | 0. 46 | 0.98 |
| 3 | 6 (2.20-13.05) | 7.92 | 3.72 | 0. 61 | 1.3 |
| 4 | 6 (2.20-13.05) | 9.9 | 4.65 | 0. 77 | 1.64 |
| 5 | 7(2.81-14.42) | 11.88 | 5.58 | 0. 92 | 1.96 |
| 6 | 7 (2.81-14.42) | 13.86 | 6.51 | 1.07 | 2.28 |
| 7 | 7 (2.81-14.42) | 15.84 | 7.44 | 1.23 | 2.62 |
| 8 | 7 (2.81-14.42) | 17.82 | 8.37 | 1.38 | 2.94 |
| 9 | 7 (2.81-14.42) | 19.8 | 9.30 | 1.53 | 3.26 |
| 10 | 7 (2.81-14.42) | 21.78 | 10.23 | 1.69 | 3.6 |
| 11 | 7 (2.81-14.42) | 23.76 | 11.16 | 1.84 | 3.91 |
| 12 | 7 (2.81-14.42) | 25.74 | 12.09 | 1.99 | 4.23 |
| 13 | 8 (3.45-15.76) | 27.72 | 13.02 | 2.14 | 4.6 |
| 14 | 8 (3.45-15.76) | 29.7 | 13.95 | 2.3 | 4.89 |
| 15 | 8 (3.45-15.76) | 31.68 | 14.88 | 2.46 | 5.23 |
| 16 | 8 (3.45-15.76) | 33.66 | 15.81 | 2.61 | 5.55 |
| 17 | 8 (3.45-15.76 | 35.64 | 16.74 | 2.76 | 5.87 |
| 18 | 8 (3.45-15.76) | 37.62 | 17.67 | 2.92 | 6.21 |
| 19 | 8 (3.45-15.76) | 39.6 | 18.6 | 3.07 | 6.53 |

(Both the assumptions that 9.4% doses (as in 15th PSUR) and the assumption that 20% doses (as in PSUR 16) were used in the second year of life are tested)

The observed deaths were significantly higher than expected for the first eight days after vaccination (except on the first day). It was significantly higher on all 20 days if we assume that 9.4% doses were used in the second year (as in PSUR 15)

The GSK explanation rings hollow with the 19th PSUR, where observed deaths in children over 1 year, in the period soon after immunization is statistically higher than ‘expected deaths’. Furthermore the deletion of deaths in the 19th PSUR seems to suggest that GSK does not plan to honestly monitor and evaluate all available data or fulfill their promise of “promptly notifying the authorities and to taking the necessary actions to communicate such data and information to healthcare professionals”.

**Relevance to India**

The regulatory authority of the Government of India is the Drug Controller General of India (DCGI). According to the DCGI rules, a drug approved in one or more countries will be considered for approval in India (8). Small bridging studies are all that is required for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen (9).

Recently there have been studies published from India looking at immunogenicity and safety of the Hexavalent combination in small trials (10,11). There have also been editorials published, entitled “Hexavalent Vaccinations: The Future of Routine Immunization?”(12) It is crucial that the regulatory authority in India is aware of the concerns raised through this commentary on the PSUR reports.

**Summary and Conclusion**

1. Von Kries (1) reported a statistically significant increased standardised mortality ratio (SMR) in children in their 2nd year of life, within two days after vaccination with Hexavac® (one of the two licensed hexavalent vaccines, now withdrawn).
2. In its periodic safety update reports GSK the company manufacturing Infanrix hexa evaluates whether the number of sudden deaths reported in this age group after vaccination with their product, exceeded the number one should expect by chance.
3. The clustering of deaths soon after immunization (see Table 1) in the infants below 1 year (93% of deaths (54 deaths), occur in the first 10 days and 7% (2 deaths) occur in the next 10 days) suggests the deaths could be caused by the vaccine.

The CEO of GSK suggests instead, that persons reporting Sudden Deaths are much more likely to think about a potential causal association and thus report an event to GSK when the event occurs shortly after vaccination than when it occurs later and this could explain the clustering. He gave an assurance that should the available data and information change to suggest that there is an increased risk, GSK remains committed to promptly notify the authorities and to take the necessary actions to communicate such data and information to healthcare professionals where Infanrix hexa is licensed.

1. It is clear from the GSK letter that ‘observed’ deaths are actually ‘deaths reported spontaneously to GSK’ (ie following passive surveillance) and are likely to underestimate the real death rate after immunization.
2. The cumulative count of deaths in the 19th PSUR is less than that in the 16th PSUR – as if some of those who had died within 20 days of vaccination, had been restored to life or declared not dead.

After the deaths already reported in the 16th PSUR were restored to the Observed/Expected analysis, in the second year (Table 3) there is a statistically significant excess of observed deaths in the first 5 days after immunization compared to expected deaths.

The manufacturer GlaxoSmithKline Biological needs to explain how 3 deaths reported within 14 days of immunization in the 16th PSUR are missing from the 19th PSUR.

1. Re-evaluating PSUR16 data (Table 4) also shows that there was a statistically significant increase in deaths observed in the second year, following immunization with Infranrix hexa.

In this PSUR 16 ‘expected deaths’ were doubled by assuming 20% of the doses were used in the second year instead of 9.4% as in PSUR 15. The observed deaths were significantly higher than expected, even after doubling the expected deaths.

1. The CEO of GSK has not informed health professionals of the risk of death as he had said he would in his letter through his chief medical officer. The increased risk is seen because the expected death in second year is 0.012/1000 and not 0.064/1000 as reported in PSUR 16.
2. Given the above, it is difficult to understand how the EMA accepted PSUR 19 at face value. As the regulator it may be argued that due diligence was not performed and thereby it exposed numerous children unnecessarily to the risk of death.
3. These facts with regard the PSUR on Infanrix hexa submitted to the EMA must be made available to the DCGI.

**References**

1. von Kries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, et al. Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilius influenzae type b): is there a signal? European journal of pediatrics. 2005;164:61-9.
2. EMEA. Press Release European Medicines Agency recommends suspension of Hexavac. Reactions. London, 20 September 2005. Doc. Ref. EMEA/297369/2005 Available at <https://lakemedelsverket.se/upload/nyheter/2005/PressmedEMEA%5B1%5D.pdf> Accessed on 12 May 2017
3. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Official Journal L – 311, 28/11/2004, p. 67 – 128. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf> Accessed on 3 May 2017
4. <http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf>
5. <http://jacob.puliyel.com/paper.php?id=395>
6. <http://www.ncbi.nlm.nih.gov/pubmed/24004825#cm24004825_8656>
7. <http://jacob.puliyel.com/paper.php?id=394>.
8. <http://www.cdsco.nic.in/writereaddata/Guidance_for_New_Drug_Approval-23.07.2011.pdf>
9. [Liu JP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Liu%20JP%5BAuthor%5D&cauthor=true&cauthor_uid=12448577), [Chow SC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chow%20SC%5BAuthor%5D&cauthor=true&cauthor_uid=12448577). Bridging studies in clinical development. [J Biopharm Stat.](https://www.ncbi.nlm.nih.gov/pubmed/12448577) 2002;12:359-67.
10. Chhatwal J, Lalwani S, Vidor E. [Immunogenicity and Safety of a Liquid **Hexavalent** **Vaccine** in Indian Infants.](https://www.ncbi.nlm.nih.gov/pubmed/27889711) Indian Pediatr. 2017;54:15-20
11. Lalwani SK, Agarkhedkar S, Sundaram B, Mahantashetti NS, Malshe N, Agarkhedkar S, Van Der Meeren O, Mehta S, Karkada N, Han HH, Mesaros N. [Immunogenicity and safety of 3-dose primary vaccination with combined DTPa-HBV-IPV/Hib in Indian infants.](https://www.ncbi.nlm.nih.gov/pubmed/27629913) Hum Vaccin Immunother. 2017;13:120-127.
12. [Shashidhar A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shashidhar%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28141560) Hexavalent Vaccinations: The Future of Routine Immunization? [Indian Pediatr.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hexavalent+Vaccinations%3A+The+Future+of+Routine+Immunization%3F) 2017;54:11-13.