Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of off-label and unlicensed (OLUL) medicines in children is common and is a potential risk factor for adverse drug reactions (ADRs).
- Previous large studies have focused on inpatients or community-based practice.
- There have been two studies which included unplanned admissions but, due to their small size, they were unable to assess properly the contribution of off-label and unlicensed medicines.

WHAT THIS STUDY ADDS

- In a study of ADR-related admissions to a paediatric hospital, the number of medicines prescribed was a predictor of risk.
- Off-label and unlicensed medicines were also more likely to be implicated in an ADR than authorized medicines, but this was driven by the higher risk of ADRs to oncology drugs prescribed in an off-label or unlicensed manner than non-oncology drugs.

AIMS

To examine the impact of off-label and unlicensed (OLUL) prescribing on adverse drug reactions (ADRs) causing unplanned admissions to a paediatric hospital.

METHODS

Prescription data from a 12 month prospective cohort study of ADRs detected in children admitted to a paediatric hospital were scrutinized. The relative risk for off-label and unlicensed medicines being implicated in an ADR was calculated. Logistic regression analyses were carried out with exposure to off-label and unlicensed medicines and number of off-label and unlicensed medicines administered as predictor variables.

RESULTS

Off-label and unlicensed medicines were more likely to be implicated in an ADR than authorized medicines (relative risk 1.67, 95% CI 1.38, 2.02, $P < 0.001$). There was a 25% increase in ADR risk (95% CI 1.16, 1.35, $P < 0.001$) with each additional authorized medicine and 23% (95% CI 1.10, 1.36, $P < 0.001$) with each additional off-label or unlicensed medicine. Logistic regression analysis focusing on non-oncology patients demonstrated that the number of authorized medicines (odds ratio 1.33, 95% CI 1.23, 1.44, $P < 0.001$), but not the number of off-label and unlicensed medicine courses, was a predictor of ADR risk.

CONCLUSIONS

In a heterogeneous population of children admitted to a secondary/tertiary hospital, off-label and unlicensed medicines are more likely to be implicated in an ADR than authorized medicines. This was largely driven by ADRs related to drugs used in oncological practice, where the usage of off-label or unlicensed medicines was associated with a higher ADR risk than in non-oncological areas.

Introduction

The risk factors for adverse drug reactions (ADRs) in children are poorly understood [1–3]. One concern has been the use of off-label and unlicensed medicines. The prescribing of a medicine off-label refers to its use outside the terms of its marketing authorization (MA) while an unlicensed medicine is one which does not have a MA in the country in which it is being used.

The reported incidence of off-label and unlicensed medicine use in paediatric practice varies widely ranging from 3.3 to 100% [1]. This variation in incidence is due to many factors including differences in study design and setting, and the definitions of ADR, off-label and unlicensed medicine used in the different studies. Interestingly, no large paediatric studies have focused solely on ADR-related hospital admissions and determined whether off-label and unlicensed medicine use was a risk factor. There have been two studies which collected data on the contribution of off-label and unlicensed medicine use to ADR-related admissions [2, 4]. However, due to the small size of these studies, their results were inconclusive. Previous larger studies have focused on paediatric in-patients [5–7] and there have also been two prospective paediatric community-based studies [8, 9]. The findings of these studies have been inconsistent. One of the inpatient studies found that off-label and unlicensed medicines were more likely to be implicated in ADRs [7], while another found no association between off-label or unlicensed medicines and ADRs [5]. Exposure to off-label or unlicensed medicines has been identified as a predictor of ADR risk factor in two previous inpatient studies [5, 6] but this was not proven in a third study [7]. In a prospective community-based study, off-label medicine use was associated with an increase in ADR risk [8].

Given the incompleteness of the data in the literature, we have investigated the association between the use of off-label and unlicensed medicines and ADRs in children admitted to hospital as part of a large prospective study of ADR-related admissions [10].

Methods

Description and setting

A 12 month prospective cohort study of unplanned admissions to a paediatric tertiary referral centre in the UK was carried out from 1 July 2008 to 30 June 2009. For each eligible patient, the study recorded the details of their medicine use in the 2 weeks before admission to hospital and identified and assessed suspected ADRs detected at the time of admission. This study used routinely collected clinical data in an anonymized format. In the opinion of the Chair of Liverpool Paediatric LREC, this study did not

require individual patient consent or review by an Ethics Committee.

Inclusion and exclusion criteria

Unplanned admissions were defined as those via the accident and emergency department (AED) and emergency transfers from other hospitals. Also included in this definition were unplanned admissions direct to wards, for example, patients under the care of the oncology unit. The study included children between the ages of 0 and 16 years 11 months.

Electively admitted patients were excluded. The study also excluded patients who presented with deliberate or accidental overdose and those in whom the misuse of medicines (prescription or illicit) was implicated.

Data collection

The methodology for data collection has previously been described [10]. Details of any medicine taken in the 2 weeks before admission were recorded: medicine name, dose, frequency, duration, whether it was a prescription or non-prescription medicine and its indication. Medicines thought to be implicated in an ADR were highlighted. Suspected ADRs were subsequently evaluated in detail and a causality assessment [11] was undertaken to determine whether each suspected reaction was unlikely, possible, probable or definite. The reactions classified as unlikely were excluded from the analysis.

Classification of medicines

The data on prescription medicine use was scrutinized in order to define each medicine course as either authorized, off-label, unlicensed or unknown. Non-prescription medicines were not classified.

A medicine course was defined as the administration of one type of medicine at least once in the preceding 2 weeks. This encompassed regular medicines, e.g. daily anti-epileptic treatment, short courses, e.g. a 5 day course of antibiotics and intermittent doses, e.g. paracetamol for fever given as required.

Authorized use was defined as the use of a medicine with a UK MA, within the terms of that MA. The terms of the MA were found in the contemporaneous Summary of Product Characteristics (SmPC) available online from the Electronic Medicines Compendium (eMC) [12].

Off-label use is the use of a medicine with a UK MA, outside the terms of that MA. A medicine was defined as off-label in this study if it was used in one or more of the following ways: for an indication not stated, at a dose above that stated, at a frequency above that stated, via a route not stated, in an individual whose age was above or below the limits stated, in an individual who had a diagnosis, history or another feature (e.g. pregnancy) which meant that use of the medicine was contraindicated and in combination with another medicine when the combination is contraindicated. With regard to age, if the SmPC

mentioned children, the definition of this was assumed to be 29 days to 18 years. If no specific information pertaining to use in neonates was provided, the use of that medicine in neonates was considered to be off-label. Medicines administered off-label for only part of the treatment course were categorized as off-label.

Unlicensed medicines were defined as those without a UK MA and could be one of the following: compounded preparations prepared in a pharmacy (including those prepared from authorized medicines), medicines manufactured under a specials manufacturing licence [13], chemicals used for treatment or diagnosis, imported medicines (which may or may not have a MA in the country of origin), medicines awaiting an MA (e.g. clinical trial medicines).

The 'unknown' category was reserved for those episodes of medicine use for which inadequate detail was available to decide whether use was authorized, off-label or unlicensed.

It was necessary to make some assumptions about some of the patients involved in the study, and about medicine use during the process of classification, because of missing information:

- weight and/or body surface area was not recorded for 63% of patients, but if it was required to check whether doses were appropriate, age-related values found in the current British National Formulary for Children (BNFC) were used [14]
- all neonates were assumed to have been born at term because gestational age was not recorded in this study
- inhalation anaesthetics were assumed to have been administered in accordance with the recommendations of the SmPC
- the classification of cytotoxic medicines was simplified by consulting the BNFC [14]. For cytotoxic medicines with a UK MA, if the BNFC monograph stated the relevant indication it was assumed that the use was authorized, if the BNFC monograph stated 'not licensed in children' the use was considered to be off-label
- it was not possible to consider the implications of dosage form manipulation by parents or nursing staff such as the crushing of tablets or the addition of licensed medicines to food or drinks for ease of administration.

Statistical analysis

The relative risk (with 95% confidence intervals (CI)) for off-label and unlicensed prescription medicines being implicated in an ADR was calculated for prescription medicines in the entire study population.

Using data obtained from the first patient admission, univariate analysis was performed to compare differences in patients with ADRs and those without ADRs and their risk factors (age, gender, number of prescription medicines, whether they were oncology patients and off-label/

unlicensed prescription medicine use). Binary outcomes were compared between groups using the chi-square statistic for assessing significance. Comparisons between groups with respect to continuous measures were made using the *t*-test or the Mann–Whitney U-test, depending on skewness, for assessment of statistical significance. The 5% level was used for assessing significance.

Regression analysis was undertaken using a logistic regression model to assess the influence of risk factors on ADRs occurring. Results are given in terms of the odds ratio (OR) for each risk factor with accompanying 95% CI.

Results

The study examined 19975 medicine courses from 6020 separate unplanned admissions from patients who had received at least one medicine course in the 2 weeks prior to their admission (Figure 1): 89% (17758/19975) of these were prescription medicines with the rest being non-prescription (2217/19975; 11%). 8% (1655/19975) of medicine courses were administered to oncology patients, three (0.2%) of these were non-prescription medications. Just two (0.09%) of 2217 non-prescription medicines were implicated in an ADR. Of the 17758 prescription medicine courses, 1207 (0.07%) could not be categorized (1183 for non-oncology patients and 24 for oncology patients) because insufficient information about the patient or the medicine had been recorded.

Of the 14923 medicine courses administered to non-oncology patients that could be categorized, 71% were authorized, 24% off-label and 5% unlicensed. Of the 1628 medicine courses administered to oncology patients, 57% were authorized, 34% off-label and 9% unlicensed. Analysis of the total 16551 categorized medicines showed that off-label or unlicensed medicines were more likely to be implicated in an ADR than authorized medicines (relative risk 1.67, 95% CI 1.38, 2.02, $P < 0.001$).

A univariate analysis (Table 1) using the prescription medicine data of patients on their first admission only (3869 patients) showed that the median age and median number of prescription medicines was greater in patients who had experienced at least one ADR. However, this was driven by the characteristics of patients exposed to off-label or unlicensed medicines. Amongst patients exposed to authorized medicines only, the median age was not significantly different between those with and without ADRs. The proportion of patient exposed to at least one off-label or unlicensed medicine was greatest amongst neonates (58.3%) and least amongst adolescents (29.5%, Figure 2). There were no neonates in the oncology population and the proportion of patients exposed to at least one off-label or unlicensed medicine was >70% in all other age categories (Figure 3). Gender was not a significant predictor of ADR risk. Logistic regression analysis (Table 2) indicated that oncology patients were more likely to

Figure 1

Medicine course categories and number of courses in each category implicated in at least one ADR

experience an ADR (OR 25.70, 95% CI 14.56, 45.38, $P < 0.001$). Each additional authorized prescription medicine course increased ADR risk by 25% ($P < 0.001$) and each additional off-label/unlicensed prescription medicine courses increased ADR risk by 23% ($P < 0.001$). Increasing age was associated with an increased risk of an ADR (OR 1.04 95% CI 1.00, 1.08, $P = 0.045$).

There were 127 non-oncology ADRs which involved a total of 198 medicines. Of these ADRs 48 (38%) involved at

least one off-label or unlicensed medicine. Of 120 oncology ADRs involving 283 medicines, 93 (78%) involved at least one off-label or unlicensed medicine (difference in proportions 40%, 95% CI 32%, 48%, $P < 0.01$). Table 3 shows the commonly used non-oncology off-label and unlicensed medicines and the frequency with which they were implicated in at least one ADR. Table 4 shows the types of off-label and unlicensed medicines most commonly used in oncology and the frequency with which

Table 1

Univariate analyses of ADRs for all first admissions by gender, age and number of prescription medicines taken (3869 patients)

Gender	All	No ADR	ADR	P value*
All boys	2247	2172 (96.7%)	75 (3.3%)	0.271
All girls	1622	1557 (96.0%)	65 (4.0%)	
OL/UL exposed boys	869	812 (93.4%)	57 (6.6%)	0.920
OL/UL exposed girls	627	585 (93.3%)	42 (6.7%)	
Authorized only boys	1321	1303 (98.6%)	18 (1.4%)	0.063
Authorized only girls	953	930 (97.6%)	23 (2.4%)	

Age (years, months) [median; Q1, Q3]	All	No ADR	ADR	P-value†
All	[3 years 1 month; 8 months, 9 years] (n = 3869)	[3 years; 8 months, 9 years] (n = 3729)	[6 years; 2 years 4 months, 11 years] (n = 140)	<0.001
OL/UL exposed	[2 years 5 months; 3 months, 8 years] (n = 1595)	[2 years 1 month; 3 months, 7 years] (n = 1496)	[7 years; 3 years 7 months, 12 years] (n = 99)	<0.001
Authorized only exposed	[3 years 8 months; 1 year, 10 years] (n = 2274)	[3 years 8 months; 1 year, 10 years] (n = 2233)	[3 years 9 months; 5 months, 8 years 6 months] (n = 41)	0.968

Number of medicines [median; Q1, Q3]	All	No ADR	ADR	P-value†
All	[2; 1, 4] (n = 3869)	[2; 1, 3] (n = 3729)	[6; 3, 9] (n = 140)	<0.001
OL/UL exposed	[3; 2, 6] (n = 1595)	[3; 2, 6] (n = 1496)	[8; 5, 11] (n = 99)	<0.001
Authorized only exposed	[2; 1, 2] (n = 2274)	[2; 1, 2] (n = 2233)	[2; 1, 3] (n = 41)	0.003

*Chi-square test. †Mann-Whitney U-test.

Figure 2

Distribution of off-label unlicensed medicine use in all patients by age (n = 3869). □, exposed to at least one OLUL medicine; ■, not exposed to OLUL medicine. ICH Classification of children by age ([21]): Preterm neonate <36 weeks gestation, 0–27 days (gestational age not recorded in our study); Neonate 0–27 days; Infants and toddlers 28 days–23 months; Children 2–11 years; Adolescents 12–17 years

they were implicated in at least one ADR. A relative risk analysis which included medicine courses administered to non-oncology patients only (3796 patients, 14 923 medicine courses) showed that the risk of an unlicensed or off-label medicine being implicated in an ADR was not significantly greater than that for an authorized medicine (relative risk 1.03, 95% CI 0.76, 1.41, $P = 0.83$). In a logistic regression analysis of the non-oncology patients, each additional authorized prescription medicine increased

Figure 3

Distribution of off-label unlicensed medicine use in oncology patients by age (n = 73). □, exposed to at least one OLUL medicine; ■, not exposed to OLUL medicine. ICH Classification of children by age ([21]): Preterm neonate <36 weeks gestation, 0–27 days (gestational age not recorded in our study); Neonate 0–27 days; Infants and toddlers 28 days–23 months; Children 2–11 years; Adolescents 12–17 years

ADR risk by 33% ($P < 0.001$). The number of off-label/unlicensed prescription medicines was not a significant predictor of ADR risk ($P = 0.627$) (Table 5).

Discussion

This is the first large scale study of the contribution of off-label and unlicensed prescribing to the risk of ADR-

Table 2

Multivariate logistic regression analysis for all first admissions (3869 patients)

Variable	Odds ratio (OR)	95% CI for OR	P value
Gender (male)	0.74	0.51, 1.09	0.130
Specialty (oncology)	25.70	14.56, 45.38	<0.001
Number of authorized prescription medicines	1.25	1.16, 1.35	<0.001
Number of off-label/unlicensed prescription medicines	1.23	1.10, 1.36	<0.001
Number of unknown prescription medicines	0.84	0.59, 1.18	0.303
Age in years	1.04	1.00, 1.08	0.045

Table 3

Off-label and unlicensed medicines used in non-oncology practice (medicines with ≥50 courses only, greatest number of courses first)

Drug	Preparation(s)	Example(s) of reason why categorised as OL/UL	Count of OLUL courses (implicated in ADR)
Metronidazole	Infusion/Oral suspension	Age	51
Gentamicin	Infusion	Dose	52
Spironolactone	Oral liquid	Manufactured special	64 (1)
Chloral hydrate	Oral elixir	Manufactured special	65 (0)
Diclofenac	Injection/Tablets/Suppositories/ /Dispersible tablets	Age, indication, manufactured special	66* (5)
Sodium chloride 0.9%	Nasal drops	Compounded in pharmacy	66
Ondansetron	Injection/Tablets/Melts/Oral syrup	Age, indication	69 (1)
Dexamethasone	Injection/Oral solution	Indication	71 (22)
Hyoscine hydrobromide	Transdermal patch	Age	79
Ibuprofen	Oral syrup/Oral suspension	Age, dose	101 (2)
Melatonin	Tablets/Modified release capsules	Import	132
Omeprazole	Tablets/Capsules	Age, indication	157
Sodium feredetate (Sodium ironedetate)	Oral solution	Indication	164
Ranitidine hydrochloride	Injection/Oral solution	Age	166
Folic acid	Oral solution	Indication	182
Morphine sulphate	Injection/Oral solution	Age	191
Paracetamol	Infusion/Oral suspension	Age, dose	288
Salbutamol	Infusion/Nebules/Inhaler	Dose	328

*2 OL tablets, 11 OL suppositories, 3 OL injection and 50 UL dispersible tablets.

Table 4

Off-label and unlicensed medicines used in oncology practice (medicines with ≥15 courses only, greatest number of courses first)

Drug	Preparation(s)	Example(s) of reason why categorized as OLUL	Count of OLUL courses (implicated in ADR)
Co-trimoxazole	Tablets/Oral Suspension	Dose	79 (0)
Ondansetron	Injection/Tablets/Oral Syrup	Age, dose	63 (1)
Levomopromazine	Tablets/Injection/Oral Suspension	Indication	67* (1)
Doxorubicin	Infusion	Age	35 (32)
Mercaptopurine	Oral Liquid	Manufactured special	34 (18)
Etoposide	Infusion	Age	28 (26)
Cyclophosphamide	Infusion	Age	25 (15)
Methotrexate	Oral Liquid	Manufactured special	24 (15)
Dexamethasone	Liquid/Tablets/Injection	Indication	23 (1)
Omeprazole	Infusion/Tablets/Capsules	Indication	19 (0)
Mesna	Infusion/Tablets	Age	18 (0)
Voriconazole	Infusion/Tablets/Oral Suspension	Indication	17 (0)
Magnesium glycerophosphate	Liquid	Manufactured special	15 (0)

*45 OL Tablets/Injection, 22 UL Suspension.

Table 5

Multivariate logistic regression analysis for all non-oncology first admissions (3769 patients)

Variable	Odds ratio (OR)	95% CI for OR	P value
Gender (male)	0.71	0.47, 1.08	0.107
Number of authorized prescription medicines	1.33	1.23, 1.44	<0.001
Number of off-label/unlicensed prescription medicines	1.04	0.89, 1.12	0.627
Number of unknown prescription medicines	0.79	0.53, 1.17	0.233
Age in years	1.05	1.01, 1.09	0.023

related hospital admissions in children. The number of patients included in our relative risk analysis of medicine courses was 6020, amongst whom 247 ADRs were detected. The number of patients included in our logistic regression analysis was 3869. A previous study which looked at the contribution of off-label medicines to ADRs on admission and in hospital included 1619 patients of whom 12 were admitted due to an ADR [2]. A more recent admissions study included 683 patients of whom 47 were admitted due to an ADR [4]. The results of the cohort study from which our data were derived indicated that patients had medicines prescribed and/or administered in both community and hospital settings, and had received an extensive variety of medicines from short antibiotic courses prescribed by a general practitioner (GP) through to intensive chemotherapy courses prescribed by specialists. Of the ADRs detected, 17.7% were attributed to community prescriptions, 34.1% were from hospital (non-oncology) prescriptions and 48.2% were from oncology prescriptions [10].

When all off-label and unlicensed medicine courses were considered together, they were more likely to be implicated in an ADR than authorized medicines. This was also seen on logistic regression analysis with each additional off-label/unlicensed prescription medicine course increasing ADR risk by 23%. Interestingly however, the number of authorized prescription medicines also increased the risk of an ADR by a similar magnitude. Given that oncology drugs were a major risk factor in causing ADRs in our study, further analyses showed that, when oncology patients were excluded, the risk of an unlicensed or off-label medicine being implicated in an ADR was not significantly greater than that for an authorized medicine and the number of off-label or unlicensed medicines was not a significant predictor of ADR risk. Our data thus show that the data from our whole population is strongly influenced by the characteristics of the oncology sub-population. It should, however, be borne in mind that the high rate of off-label and unlicensed medicine use in paediatric oncology settings, may reflect evidence-based protocol recommendations for specific oncological diseases. Moreover, these recommendations anticipate toxicity and recommend measures to manage the effects.

How do our findings compare with previous studies? In two previous studies of ADR-related admissions, one iden-

tified 12 ADRs of which five involved an off-label medicine [2] and the other identified 47 ADRs of which 20 involved an off-label or unlicensed medicine [4]. Neither study was large enough to prove or disprove a relationship between off-label and unlicensed medicine use and ADR risk. In terms of community-based and inpatient studies, there are contradictory data in the literature. Thus, while some studies have shown that off-label and unlicensed medicines are a risk factor for ADRs [6–9], other have not [2, 5]. There are many reasons for the contradictory findings. First, the study settings have varied; some have focused on admissions [4], some have included only inpatients [5–7], others have used a combination of in-patients and new admissions [2], while others have been community-based [8, 9]. There is some evidence that off-label prescribing is more prevalent in children who receive a greater number of prescriptions from their GPs, and in those who require a greater number of referrals to specialist care, and indeed in specialist care *per se* [15, 16]. Second, given the differences in study settings, the types of patients surveyed have been different. Thus, in our study, oncology patients were a major sub-group evaluated and indeed a significant predictor of off-label and unlicensed usage. Only one previous study included oncology patients [4]. Third, and this is of course connected to the type of patients studied, is the type and number of medicines evaluated. Our study represents the largest number of medicines surveyed to date, and thus represents the spectrum of paediatric practice. This also allowed us to consider a wider breadth of off-label and unlicensed prescribing. A small study with a narrow range of medicines is likely to lead to biased findings. For example, weight-based paracetamol doses which are off-label because they exceed the age-based doses, are highly unlikely to cause ADRs, whereas an anti-cancer drug has a narrow therapeutic window, and any deviation in dose, may lead to an ADR. Fourth, the definitions of off-label and unlicensed medicines have varied between different studies [17]. For example, Kramer *et al.* examined only one aspect of off-label use, the administration of a total daily dose greater than that recommended by the manufacturer whether prescribed or secondary to parental over-treatment. The latter, however, could be considered an error rather than off-label use [9].

The number of authorized and off-label or unlicensed medicines were both predictors of ADR risk, an aspect not

examined by previous studies. This suggests that the number of medicines is a more important predictor than whether they are authorized or not. Indeed, previous studies in both adults and children have identified number of medicines as an ADR risk factor [5, 7, 18–20]. We can hypothesize that a patient who receives more medicines is likely to be more unwell or have more complex disease(s) and so there will be increased potential for drug–disease and drug–drug interactions and consequent ADRs in that individual.

Our study has several limitations. We required a minimum amount of information to be available about the use of a medicine before it could be categorized as off-label. The absence of this information was a result of how drug histories were recorded on admission. Further limitations are the assumptions outlined in our methodology which pertain to the SmPC definitions of age, gestational age and the classification of cytotoxic medicines.

In summary, in a heterogeneous population of children admitted to a secondary/tertiary hospital, off-label and unlicensed medicines are more likely to be implicated in an ADR than authorized medicines. This was largely driven by ADRs related to drugs used in oncological practice, where the usage of off-label and unlicensed medicines was associated with higher ADR risk than in non-oncological areas. Indeed, analysis of the non-oncological drugs showed that exposure to an off-label or unlicensed medicine did not significantly increase ADR risk. Most importantly, both the number of off-label, unlicensed medicines and authorized medicines were significant predictors of ADR risk. Our study highlights an important issue in paediatric practice. While there is always quite rightly concern about the use of off-label and unlicensed medicines in children, we need to be clear about when this corresponds to the use of medicines off-knowledge and the clinical implications of this. There is a need to improve the study of drugs in children, not only those which are currently considered off-label or unlicensed but also those which are authorized, with a view to improving the posology of drug administration, in particular dosage, which is hugely important in determining both efficacy and safety.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare JRB, JJK, AJN and MP had support from the NIHR (see below) for the submitted work. AJN is a member of the EMA Paediatric Committee and a member of the MHRA Paediatric Medicines Expert Advisory Group. MP is a NIHR Senior Investigator and a member of the CHM, chair of the Pharmacovigilance Expert Advisory Group.

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