

# Present era of drug safety in India: An overview

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## Abstract

Date Received: 04/12/2020 Date Revised: 09/01/2021 Date Accepted: 28/01/2021	<p>Common Adverse Drug Reactions (ADR), evaluated by drug clinical trial studies, whereas an individual or specific population might suffer reactions after prolonged dormancy. Pharmacovigilance (PV) is a scientific investigation dealing and keeping regular vigil on the drugs being used. The Indian Pharmacopoeia Commission (IPC) and other regulatory authorities like a National Coordination Committee (NCC) via the Central Drug Standard Control Organization (CDSCO) manage PV activity in synchronicity. Indian Pharmacovigilance (PV) system require carving, therefore the Pharmacovigilance Program of India (PvPI) was enforced by the government in the year 2010, relying on exact ADR detection, evaluation and reporting. Thus, several regional, zonal and peripheral centres are developed for ADR reporting. Clinicians, Nurses, layperson, pharmacist and other healthcare professionals can fill ADR reporting form online or offline at the nearest centres in suitable languages. Additionally, a toll-free number and mobile app could be used for reporting ADR. Every reported ADR gets collected and processed at the centres through Vigi-flow software, which detects and assess the signal strength reported at CDSCO and World Health Organisation (WHO) for the required regulatory action. The final decision of CDSCO-WHO is passed by a suitable media source for the advancement of society's health.</p>
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## Introduction

Pharmacovigilance (PV) importance comes under focus for the first time in December 1961, due to a peculiar publication in the Lancet journal, correlating serious foetal abnormalities like phocomelia with a renowned drug 'thalidomide' (used during pregnancy) by W. McBride (Australian physician). Thalidomide exhibits antiemetic and sedative actions in pregnant ladies. World Health Organization advertised the "Programme for International Drug Monitoring", a pilot project aiming to centralize world data on adverse drug reactions in 1961 (Atif et al., 2020). "WHO Programme" aims at the initial stage identification of the PV signals. During 70s, a French group of pharmacologists and toxicologists coined the term "Pharmacovigilance", representing "Evaluation of the risks or potential side effects linked with treatment (Suke et al., 2015).

Collectively, the clinical trial statistics reflects the safety parameters and efficacy of a drug and its market success. Usually, the clinical trials are conducted in a limited numbers and on the controlled population and only the common adverse effects get outlined (Suvarna, 2010). However, in specific individual the peculiar reaction develops after protraction, which remained non-detected/dormant initially. The reason relying behind this might be specific genotype and specific physiological properties (Evans and Relling, 1999). If any medicine is needed to be considered safe, critically for this the beneficial effect must be greater than the associated risk (Stiller, 2007). Particularly, to determine the complete safety profile of medicine/drug; a persistent evaluation and monitoring in various different populations are essential, which is vital in terms of drug safety or Pharmacovigilance (Jordan et al., 2010). PV deals with the study of drug-related adverse effects and as well as adverse events and other drugs associated problems

(Aranaz-Andrés et al., 2012). All chemicals other than the food that can influence biological systems and react with the pathological state of the disease are called drugs. So, if it produces harmful or toxic effect then it is considered the toxicity associated with the drug (Brekman, 2013). Intriguingly, every drug can be labelled toxic, if it gets utilized at the toxic dose (Shende et al., 2015). Whereas, the noxious and unintended reactions observed at normal therapeutic dose are considered 'Adverse Drug Reactions' (ADRs). Furthermore, the "Adverse events" are the unfortunate events, which emerges during the drug treatment period and are not directly interlinked with the drug use (Alam et al., 2018).

### Thalidomide Tragedy

Thalidomide was initially launched in market during the late 1950s for sedation along with management of nausea especially within pregnancy span (Eriksson et al., 2001). Intriguingly, in different countries like Australia, Japan and Europe where this drug was used for few years, resulted in above 10,000 casualties of children born with phocomelia. Therefore, it got banned for first time from markets of various countries during 1961. Henceforth, few countries reluctantly provided thalidomide for upcoming couple of years. Besides to limb abnormalities, thalidomide is also associated with congenital heart disease, inner and outer ear malformations along with visual dysfunctions (Daemmrich, 2002). Dr Frances Kelsey who worked in U.S. Food and Drug Administration spurn the thalidomide tragedy by holding on to its approval, later on President John F. Kennedy notified her credential work, making her as a deserving recipient of the Gold Medal Award for acclaimed public Service. Although, her decision to hold on the thalidomide approval was not interconnected with birth defects, but rather it was associated with peripheral neuropathy and the potential effects of drug after treatment of pregnant women, because until that period of time there was no clear evidence or reports associating the birth defect and thalidomide use (Daemmrich, 2002). Interestingly, her concerns highlighted the thalidomide tragedy, but it also drew the attention towards the requirement of harsh and relevant testing prior to the drug introduction into the marketplace along with monitoring of pharmaceutical industries. Initially, it was Josef Warkany, the creator of the Teratology Society, who conjectured in 1962 that thalidomide utilization was behind the limb defects epidemics. He found that the experimental rat developed comparatively less percentage of malformations than in humans (i.e., mothers who were treated with thalidomide, some had normal children and in some malformations occurred in children) (Löwy, 2017). The thalidomide episode leads to the acceptance of requirement for the systematic analysis of pharmaceutical related products for their toxicity clearance prior introducing into the market. The thalidomide tragedy leads to the flourishing of the detailed testing protocols along with monitoring upgrades

(Ashburn and Thor, 2004; Stolley and Strom, 1986). The thalidomide tragedy further pointed at the species variability based on the sensitivity and reactivity. At the early stages of developmental the pharmaceutical products toxicity testing must be carried on two species, one of which should not be a rodent. Although, data obtained from the rat species is quite good for evaluation, supporting the notion that use of a single species for data collection might be good enough for approving a drug (Chapman et al., 2013).



**Figure 1:** Effect of Thalidomide

### Evolution of PV

Before the 1950s and 1960s the health care regulations were very lenient and instead of drug safety, the efficacy of the drug was preferred (Neill, 2014). In 1961, phocomelia was result of thalidomide tragedy, which compelled the authorities to develop a system to assure the drug safety (Timmermans and Leiter, 2000). In 1968, the World Health Organization (WHO) initiated the international drug monitoring program, to ensure the drug safety profile globally in systematic manner and to resolve its related issues (Amale et al., 2018). During the mid-70s a French scientists coined the term pharmacovigilance, which primarily focuses on identifying the harmful effect of drug therapy (Suke et al., 2015). Since the 19th century, a numbers of medicines have been introduced in the market as safe and effective outlying the numerous analysed drugs. From previous literature it is evident that approximately all drugs manifest beneficial effects accompanied by some adverse effects. ADR is prevalent term used in pharmacology. To minimize ADR, Pharmacovigilance came to rescue by evaluating and monitoring ADR in order to safeguard society health (Organization, 2002).

**Table 1:** Major induced toxicities reported post marketing surveillance

Year	Drug	Adverse drug reaction
1937	Sulphanilamide	Renal failure
1950	Chloramphenicol	Aplastic anemia
1961	Thalidomide	Phocomelia
1970	Practolol	Oculo-mucocutaneous
1970	Clioquinol	Subacute-myelopathic, Neuropathy.
1980	Benoxaprofen	Hepatic and renal failure
1980	Doxylamine	Fetal malformations

1990	MMR(Vaccine)	Autism
1995	Oral contraceptives	Venous thromboembolism
2004	Rofecoxib	Myocardial Infraction
2012	Rimonabant	Convulsions, Suicidal tendency

### Scope of PV

PV is a prosperous and grooming concept, which deals with various fields such as Allopathic, Herbal and Unani medicines. The information about the suspected product such as- medicine or medical devices gets collected by healthcare professionals and patients, who detect ADRs and prevent associated teratogenicity (Pal et al., 2013). Accordingly, Pharmacovigilance deals with monitoring and evaluation of adverse effects of the drugs, poly-pharmacy, paradoxical reactions, and severe adverse events. Pharmacovigilance deals in different fields like failure of vaccination, irrational use of medicine, drug-drug interactions, poisoning, overdosing, lack of therapeutic effects and medication errors, misuse or abuse of the drugs (Karimian et al., 2018).

### Significance of PV

A newly developed medicinal molecule introduced in the market without long term safety studies may not claim to be the pharmacologically safe and effective and may possess harmful or poisonous effects (Boullata and Nace, 2000). Formerly in India, the safety evaluation of drugs was based on the prolonged administration of that drug. But this practice was unpredictable and failed to assert the complete safety (Smith, 2001). Taking this fact into account, the number of Indian organizations or research funding bodies initiated the drug research and launching new medicine or medical device and monitoring there use in individual (Sobanjo-ter Meulen et al., 2019). Once a product get developed, new information relate to product emerges which might be beneficial or negative, impacting its risk-benefit profile. This newly generated information gets assessed by the aid of the PV system, re-ensuring the public health. The drug associated adverse effects could result in morbidity or mortality and therefore a systematic study is required to attenuate the risk factor and to enhance the benefit (Organization, 2006). Due to recent high-profile drug withdrawal cases, the pharmaceutical companies and regulatory authorities are strictly focussing on the safety monitoring of drugs in the market (Eichler et al., 2008).

India has attained 4th rank in global pharmaceutical productions. Presently, more than 6,000 authorized manufacturers along with 60,000 brands of medicine are available all over in the Indian market. Intriguingly, usually the patient uses two or more medicine simultaneously, which could be prescribed or non-prescribed medicine increasing the chances of the drug-

drug interaction along with the ADRs (Sawarkar et al., 2019). So, to avert this condition and care for the patients from potential toxic effects caused by new or existing drug there is a need to improve the PV system in India. The PV personnel do strict surveillance of ADRs and communicate the exact results with stakeholders as a preventive measure to ensure the drug rational utilization (Quartey and Retnadhas, 2016). Till now PV had not achieved its top-notch level as an academic specialty and in present era of clinical pharmacology, pharmacy exhibits the incompetency to cover important PV skills. Currently, Indian companies are putting their faith and investing in researches concerned with the pharmacological molecule development. Furthermore, due to the fact that India has huge population, the participants number in clinical trials are also large, therefore India has huge potential in clinical research field. Formerly, the new drugs were developed in other countries and therefore took more time to get avail in market of India. PV ensures the population health by notifying the drugs associated risk factors and ADRs severity, thus avoiding further unanticipated toxic effects (Rao et al., 2012).

### PV Program of India

During 1986, a formal ADRs monitoring system owning nearly 12 centres was developed along with other special consideration on the PV activity. During year 1997, India also joins the WHO launched ADR Monitoring Program which was organized at Uppsala monitoring center (UMC), Sweden. Although, this mere participation was not sufficient for improving the PV functioning. Therefore, on 14th July 2010, the Indian Government launched the PV Program for India (PvPI). All India Institutes of Medical Sciences (AIIMS), New Delhi is elected National Coordinating Centre (NCC), working for safety and public health by monitoring and evaluating the products safety as a part of PvPI. During year 2010 it was reported that there were 22 established AMCs. The NCC was relocated in IPC, Ghaziabad from AIIMS, New Delhi on day 15-April 2011 for ensuring feasible and effective performance of the program. The determined number of medical colleges, hospitals and centres fulfilling necessary eligibility criteria were approved as ADR Monitoring Centres (AMCs). These AMCs gather data from the Individual Case Safety Reports (ICSRs) and carries out the report analysis procedure. Once, it become clear that a received case is genuine than it gets communicated further to regulatory authority. Presently, around 250 AMCs (government and non-government) have been established under PvPI. Additionally, for the purpose of spontaneous ADR reporting, there are total of 20 Anti- Retroviral Therapy (ART) and 17 Revised National Tuberculosis Program (RNTCP) centres all over the country. The technical assistance and associate from Medical colleges like Banaras Hindu University, is an approved and certified person for gathering ICSR, additionally they carry out its follow up and entry in online database called

Vigi-Flow software. Every community health centers (CHCs) and primary health care centres (PHCs) pass on their gathered ADR reports to the regional center. Tantalizingly, it is believed that the herbal or natural treatment is comparatively safer and lack of any ADR. However, "Charka Samhita" the backbone of Ayurveda and its alternative systems exclaims that polyherbal

formulations can also instigate ADRs, in peculiar circumstances where the dispensed formulation is compounded and dispensed clumsily. Therefore, it is highly recommendable to develop PV system for Ayurveda, Siddha and Unani (ASU) in order to gather and provide ADR data of AYUSH drugs as per the guidelines of WHO (Prakash, 2007).

**Table 2:** Historical Development of PV in India

Year	Initiative	Year	Initiative
1996	India started a global standard clinical trial.	1997	India joined ADR Monitoring Program.
1998	PV activity initiated in India.	2002	67th National Pharmacovigilance Centre established in India.
2005	India started conducting structured clinical trials.	2009-2010	The PV plan of India was initiated and implemented.

**Table 3:** List of ADR reporting status 2019 (PvPI) and suspected drug

S.No	Suspected Drug	Indication	Adverse Reaction
1.	Miltefosine	Directly Observe Therapy of visceral Leishmaniasis caused by Leishmania donovani	Acute Pancreatitis
2.	Dabigatran	For the prevention of stroke, systemic embolism, and reduction of vascular mortality in adult patients with atrial fibrillation.	Alopecia
3.	Sertraline	Major depressive disorders, Obsessive Compulsion Disorders (OCD), panic disorders	Maculopathy
4.	Amiodarone	In the treatment of control of ventricular and supraventricular arrhythmia where another drug cannot be used, arrhythmia is associated with the wolf-white syndrome. For cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock.	Acute Pancreatitis
5.	Teicoplanin	Glycopeptide antibiotic-use in serious gram +ve infection, staphylococcal infection in patients sensitive or unresponsive to penicillin and cephalosporins CAPD related peritonitis, prophylaxis in orthopedic surgery at risk of gram +ve infections.	Red Man syndrome
6.	Febuxostat	For the treatment of chronic hyperuricemia in conditions where urate crystals deposition has already occurred (including a history, or presence of tophus and /or gouty arthritis).	Toxic Epidermal Necrolysis/Stevens-Johnson Syndrome
7.	Netilmicin	Aminoglycoside antibiotic - Indicated in the treatment of septicemia including neonatal sepsis and other severe systemic infections.	Tetany
8.	Metronidazole	For the treatment of amoebiasis, urogenital trichomoniasis & giardiasis.	Vasculitis
9.	Risperidone	Indicated as monotherapy or as adjunctive therapy in lithium or valproate for the maintenance treatment of Bipolar-1 disorder	Rabbit Syndrome
10.	Teneligliptin	For the treatment of type-2 Diabetes Mellitus as a monotherapy adjunct to diet and exercise.	Arthralgia
11.	Atorvastatin	As an adjunct to diet to reduce elevated total cholesterol & triglyceride level in patients with primary hypercholesterolemia & mixed dysbetalipoproteinemia (Type IIa & IIb)	Vit-D deficiency

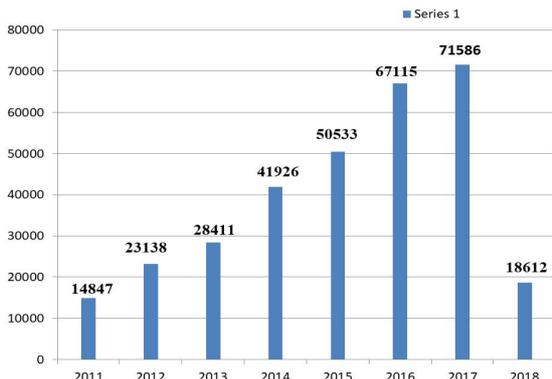


Figure 2: Year-wise ICSR reporting status 2011-2018

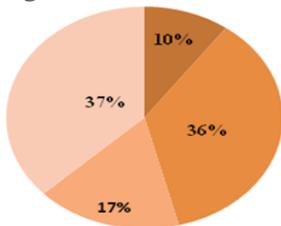


Figure 3: Zone-wise AMCs

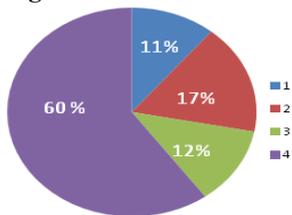
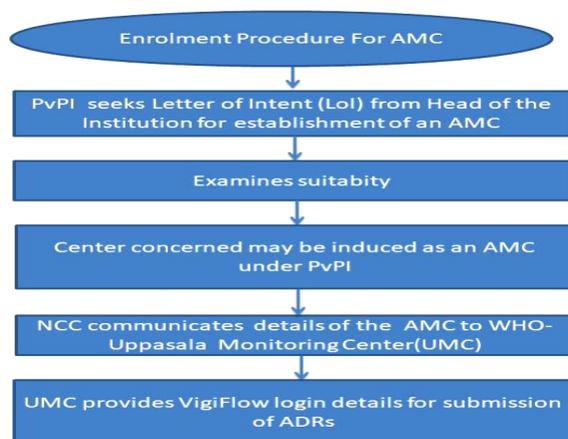


Figure 4: Break-up of Reporters contribution to ADRs



Flow chart 1: Establishment of AMCs under PvPI

### Criteria for enrolment of AMCs (ADR Monitoring Centres)

- Availability of logistics and infrastructure facilities for PV at the Centre
- Maintained track-record of the quality, quantity and frequency of Adverse Drug Reaction (ADR) reported at pharmacovigilance centre.
- States where no or few AMCs exist are given preference

- HOD/Dean/Principal of the institute designates the new AMC coordinator
- HOD/Principal of a centre create or implement PvPI functioning at the Centre
- Significant track-record/expertise of the proposed AMC coordinator/deputy coordinator in Pharmacovigilance

### Who can enroll as AMC?

- Government hospitals/Medical colleges
- Private hospitals
- Corporate hospitals
- District/primary Health Centre

### Criteria for ADR and its Reporting to Regulatory Authority

#### What to report?

Following events can be reported to the authority of nearest reporting centre

- Life-threatening event or death
- Hospitalization of the patient
- Congenital anomaly
- All suspected drug interactions
- Lack of efficacy connected with the use of a medical device or drug product.
- Medically significant event physician considering event serious)

All known or unknown, serious, non-serious, frequent or rare reactions caused due to use of vaccine or drug must be reported.

#### When to report?

- All spontaneous cases should be reported within 10 days.
- All suspected ADR should be reported as fast as possible, because over-reporting is always better than under-reporting.
- Death event must be reported as soon as possible, while all other serious ADR/event needs to be reported within 7 days.
- All non-serious cases must be reported within 30 days.

NOTE: Reporting delays might create a serious problem.

#### Who can report?

Professionals working in the healthcare team are the preferred source of information in PV, for example:

- Medical specialists/clinicians
- Nurse/Midwives
- Pharmacists
- MPHW
- Dentists
- Paramedical Staff

- Non-healthcare people include: Patient, Patients relatives, witness or any common person

### How to report?

- Duly filled ADR reporting form is to send to the nearest ADR Monitoring Centre (AMC) or directly to the National Coordinating Centre (NCC).
- Dial toll-free helpline number-1800 180 3024 to easily report ADRs.
- By mailing the filled ADR reporting form directly to [pvpi@ipcindia.net](mailto:pvpi@ipcindia.net) or [pvpi.ipcindia@gmail.com](mailto:pvpi.ipcindia@gmail.com).

One can directly log on to the <http://www.ipc.gov.in>, [http://www.ipc.gov.in/PvPI/pv\\_home.html](http://www.ipc.gov.in/PvPI/pv_home.html) for a list of authorized AMCs of India.

### Where to report

A large Number of Peripheral, Regional and Zonal centers have been established in India.

*Peripheral PV center:* It is a primary ADR information caucus center. It includes small medical centres, private hospitals, dispensaries, nursing homes, and pharmacies. ADRs are recognized and adjust by RPCs or ZPCs. Every state, Union territory and few dominant medical colleges in India have also this peripheral center.

*Regional PV center:* It's noticed as a secondary PV Centre. It is located in medical college having relatively larger expertness. They are checked and coordinated by zonal centers. There are five such regional centres in India.

*Zonal PV centers:* Its view as Tertiary PV Centre. Generally, medical college situated in the metro city's has an attachment of sufficient facility. It is controlled by CDSCO and acts as the first ADR data collection centre. Zonal center for North and East zone is AIIMS.

### List of Central Drug Standard Control Organisation

(CDSCO) Zonal and Sub-Zonal Offices

- Zonal Centre-Ahmadabad
- Zonal Centre-Hyderabad
- North Zonal centre-Ghaziabad
  - a) Sub-Zone Office-Ghaziabad
  - b) Chandigarh,
  - c) Sub-Zonal Office, Jammu
- East Zonal Centre-Kolkata-Air Port and Sea Office, Kolkata
- West Zonal Centre-Mumbai-Air Port and Sea Office, Mumbai, Jawaharlal Nehru Port Office, Navi Mumbai
- South Zonal Centre-Chennai
  - a) AirPort and Sea Office,
  - b) Sub-Zonal and Port Office, Chennai
  - c) Port Office, Kochi-Bangalore.

### Roles and Responsibilities of In-Charge Personnel at PVPI

- The Co-ordinator is responsible for the smooth and justified functioning of AMC, the charge for the same during the absence of coordinator gets shifted to sub-coordinator.
- AMC must appoint a technical associate, responsible for the collection, follow up, reporting, scrutiny, analysis and records of ADR into the Vigi-Flow database. As per SOP all processes are carried out and the final evaluation is done by NCC.
- AMC in-charge is responsible to send ADR status reports to NCC on monthly basis.
- The center coordinator at PvPI is responsible for creating awareness and guiding the HCPs, students and patients about ADR reporting by taking lectures, advertisement through email, telephone, pamphlet, and newsletters.
- At last AMC coordinator has an additional duty for Feedback collection and communication to the HCPs.

### The challenges of PV in India

The basic trouble of the Indian PV system is nationwide common populations ADRs related little awareness, underreporting, and carelessness about PV in HCPs. Population in India generally ignore minor reactions which might produce a harmful effect in the future. HCPs are little enthusiastic towards PV due to the unavailability of sophisticated and good instruments, basic facilities, the gap between guidelines and laws, are some other various difficulties. Currently, the regulatory inspections in PV sectors are not focused on achieving the up to mark functioning. India has the expertise brain in IT, hence the PV system may get furnish with the help of PV experts working in alliance with the IT sector. This teamwork may build a booming database or software, which might gather, analyse, monitor and process number of ICSRs and ADR reporting forms precisely at high speed. DCGI and other health authorities must invest and take regulatory responsibilities to build an all-inclusive PV setup and database. These databases should be cost-effective and user-friendly, used by different IT companies, to process PV cases rapidly. Presently, India is struggling to grow and improve in this sector for which industrial and regulatory involvement is required. Every time the patient could not visit the physician, hence pharmacist and other HCPs should be trained enough to monitor and communicate the ADR to AMC. Unfortunately, ADRs might go undetected from the physicians during hospital admission, leading to future blunder and deaths.

### Impact of PV

NCC has worked well to improve knowledge of HCPs about the reporting of ADRs and making them competent. Impact of PV is fruitful by reporting more than 149000 ADRs to CDSCO. Presently, part of India is nearly 3 % of

the complete WHO global ICSR databases. The primary SUASAR evaluation from the PvPI database in 2017 reveals that Cefepime, Losartan, Amisulprid leads to health risks. Previous post-marketing data expose that reporting of toxicities or adverse effects of the drugs lead to the improvement of patient safety and avoidance of harmful effects followed by suspect drug withdrawal from the market in world.

### Conclusions

The pharmacovigilance system in India has increased awareness in public about ADR reporting. The issues like underreporting are no longer a problem as a large no. of reporting skills like toll-free dial number, ADR form available in various languages, Email ids are available for public access. Several multinational companies are involved in the PV activity as outsource in India which is building up a good PV environment. A large number of universities have started PV courses in their curriculum as compulsory or elective subjects to make healthy India. Government of India needs to spotlight on the awareness and amplification of pharmacists' knowledge and providing them facilities and rights to conduct PV activity. Specialized PV cells must be established in each Hospital to monitor and assess the ADR. In future, India may become a centre for outsourcing PV, for global PV activity, considering motivational approach of HCPs, role of Clinical Pharmacists and advancements in the PV sector for ADR evaluation and involvement of large number of Pharma companies in Pharmacovigilance activities. Pharmacovigilance officer can play key role to ensure availability of safe drugs in market in future.

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### Conflict of Interest

The authors declare no conflict of interest, financial Or otherwise.

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