POSITION PAPER

Position Paper PP-01 – September 2006

Good Manufacturing Practice Guide for Medicinal Gases – AIGA 023/05

1 Introduction

A Medical Work Group (MWG) was set up in AIGA to assist its members to achieve AIGA objectives in the medical gases industry, by providing a forum where the members can share their accumulated experience in the safe handling and use of medical gases.

The goals are:

- To promote general safety, health and environmental awareness in the **manufacture and distribution** of medical gases, and to achieve continuous improvement in these areas.
- To provide national associations with medical gases guidelines and information to promote the development of local standards.
- To promote harmonisation of standards in the respective countries and across Asia.

The first project of the MWG addresses good manufacturing practice (GMP) for medicinal gases.

The principles of GMP are defined in AIGA document 023/05, "GMP Guide for Medicinal Gases", (adopted from EIGA document 99/03, "GMP Guide for Medicinal Gases")

AIGA recommends that the national associations adopt this GMP and develop their own programmes for its implementation.

This document contains the first set of guidelines for the interpretation of the full GMP document. The entire process is to be seen as one for continuous learning and improvement. It will take a number of years for the GMP process to be in place as a "full" GMP.

2 Prioritisation – Core elements of GMP

Implementing the GMP across Asia is a long-term objective and is envisaged to be a massive effort over a number of years.

AIGA document 023/05 consists of about 200 guidelines. It would be difficult and impractical to address all the requirements at once. It is therefore necessary to have a simplified strategy to progress step by step.

The MWG recommends prioritising sections in the GMP guidelines as a first step. The next step is to define the different stages of progress.

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Accordingly, core elements are highlighted as the heart of the GMP. For a start, the minimum standards that are to be achieved are indicated against each of the core elements. These are listed in Table 1.

3 Implementation – guidelines for national associations

3.1 General principles: local Implementation of GMP (AIGA guidelines)

(See Figure 1: Flowchart for implementation of GMP for medicinal gases)

3.1.1 Carry out a gap analysis

Where relevant local regulatory systems and standards exist, the national association should review these against the AIGA guidelines. If the existing regulatory systems and standards are not sufficient to implement the AIGA guidelines, or contradict them, the national association should **determine** the changes necessary to implement the AIGA guidelines locally.

If local regulatory systems and standards do not exist, the national association should **draw up** guidelines on the priority regulatory systems and standards that should be developed, and develop drafts of these to propose to the relevant local authorities.

3.1.2 Define and implement a national regulatory strategy to support the AIGA guidelines

Once the gaps are known, the national association should identify the key governmental and other groups with the power to make the necessary changes to incorporate the AIGA guidelines into the national regulatory frameworks.

The national association should then convince the relevant local regulatory authorities to adopt the principles of the AIGA guidelines.

- The first objective is to convince the local authorities that the AIGA guidelines are of value, and come to a common understanding of the current situation.
- The second objective is to agree with the relevant authorities where the gaps and/or deficiencies within the existing regulatory systems and standards are, relative to the AIGA guidelines, and to have the necessary changes incorporated into those systems and standards.

3.1.3 Define the implementation approach

The AIGA guidelines may be relatively easy to implement immediately. For example:

- The national association may quickly decide on implementation of the AIGA guidelines.
- Implementation of the AIGA guidelines may have minimal cost impact.
- Existing regulatory systems and standards may already be in place.

In this situation, the national association should aim to convince the relevant regulatory authorities that the necessary regulatory changes identified in the gap analysis should take place in full, as soon as possible.

However, in other situations, it may be unrealistic to implement the full AIGA guidelines immediately. For example:

- The national associations may not be able to adopt all aspects of the AIGA guidelines.
- There may be significant cost or other difficulties with implementing the AIGA guidelines.
- The country may not have appropriate regulatory systems and standards.

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In this situation, there should be no compromise on the elements of the AIGA guidelines, but there can be flexibility on how long it takes each country to comply with the guidelines. The national association should develop a suitable implementation phasing and time period which would enable the complete implementation of the full AIGA guidelines.

In developing the implementation plan, the national associations should ensure that the high priority issues are addressed as early as possible in the implementation time frame. These priorities will vary by country, depending on factors such as the current situation in each country, the difficulty and costs of implementation, and the regulatory environment.

3.1.4 Voluntary adoption of the AIGA Guidelines by the national associations

The regulatory strategy of the associations should seek to embed AIGA guidelines within the national regulatory frameworks to set long term ground rules that ensure all current and future organisations involved in medical gases comply with the minimum safety standards recommended by AIGA.

However, this does not mean that AIGA member organisations must wait until AIGA guidelines have legal status before adopting them. In parallel with the regulatory approach, the national associations should develop an implementation phasing and time frame within which each member organisation will voluntarily comply with the AIGA guidelines, where permitted by local laws and regulations.

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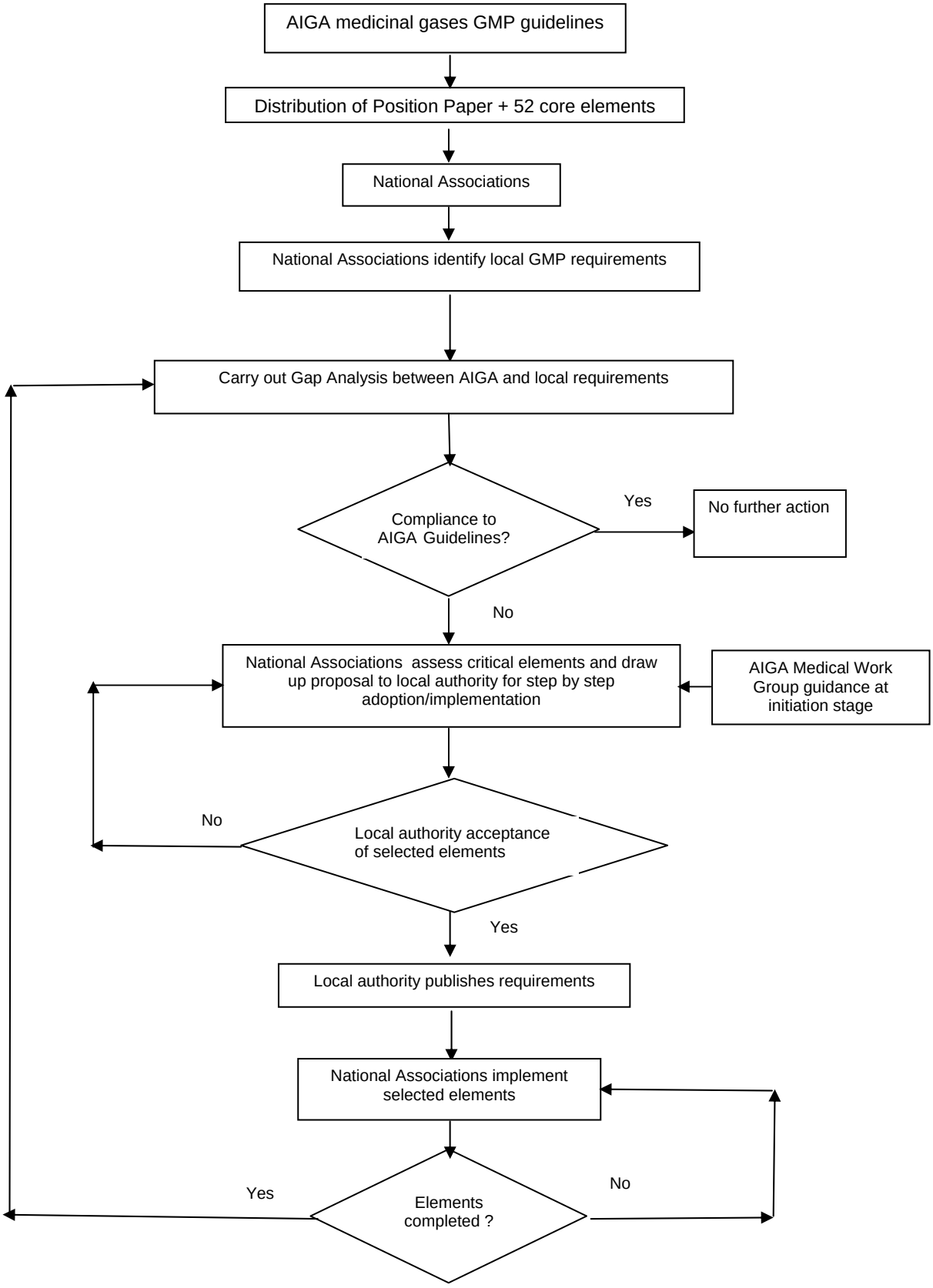

Figure 1: Flow chart for implementation of GMP for medicinal gases

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4 Core elements of GMP and minimum standards

Table 1: Core elements of GMP and minimum standards for implementation in phase 1

	GMP Core Element	Phase I Minimum Standard	AIGA GMP Guide Reference (Doc 023/05)
1	(Quality System) Leadership and administration	Quality policy established and senior management responsibilities defined.	4.1 Principle; 4.2 Quality Assurance; 4.3 GMP for Medicinal Gases; 4.4. Quality Control
2	(Quality System) Quality Control Responsibilities	QC roles and responsibilities defined and clearly allocated to staff.	5.3.4 Person Responsible for Quality Control; 9.2.1 Quality Control Responsibilities
3	(Quality System) Quality Training	Nominated quality officers (not necessarily dedicated) trained in basic quality policy and systems.	5.1 Principle; 5.3.4 Person Responsible for Quality Control; 5.4 Training
4	(Quality System) Standards Management	Local standards and record management procedures cover all medical production sites and critical medical processes and records.	7.1 Principle; 7.2.2 Work instructions; 7.2.3 Standard Operating Procedures; 7.2.4 Batch Records; 7.2.5 Document Control; 7.3 Specifications
5	(Quality System) Material Selection	Material selection procedures in place, including a review of material compatibility and risk of potential contamination of medical products.	6.8.2 Material Selection; 8.3.5 Change Control
6	(Quality System) Calibration	Critical QC instruments identified and calibration procedures in place.	6.8.3 Calibration; 7.5.5 Cylinder Filling Batch Record; 7.6.6 Records; 9.2.5 Quality Control Documentation
7	(Quality System) Traceability and Record-keeping	Product conformance to specification is recorded and linked to batch number.	7.2.4 Batch Records; 7.4.4 Medicinal Cylinders Filling Procedures; 7.6.5 Batch Distribution Records; 8.5.7 Traceability (bulk); 8.6.2 Traceability (cylinders)
8	(Quality System) Product Specification	Product specifications defined and communicated to customers for all medical gases and either comply with or exceed local regulatory requirements.	7.3 Specification; 7.3.3 Bulk medicinal Gases; 7.3.4 Finished Medicinal Gas
9	(Quality System) Packaging Materials - Labels	Systematic controls are in place on label storage, label issuing, and control of obsolete labels.	8.8.1 General; 8.8.2 Label and Leaflet Supplier; 8.8.3 Label and leaflet Storage; 8.8.5 Obsolete Labels; 8.8.7 Label Quality; 8.8.8 Unused Labels
10	(Quality System) Supplier Approval	Written contracts are in place with each supplier for production, analysis and technical arrangements.	8.4.2 Suppliers; 9.2.4 Quality Control Requirements
11	(Quality System) Equipment / Raw Materials Procurement	Specifications for critical production equipment and materials are defined and applied during procurement.	7.2.1 Starting Material; 8.4.2 Suppliers;
12	(Quality System) Regulatory Compliance	Systems in place to identify relevant regulations, manage compliance, and monitor changes.	4.1 Principle

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	GMP Core Element	Phase I Minimum Standard	AIGA GMP Guide Reference (Doc 023/05)
13	(Quality System) Self Inspection	Regular self-inspections are carried out to review performance of the Quality Assurance system.	12.1 Principle; 12.1.1 Self Inspection Programme; 12.2 Self Inspection Audits; 12.3 Self Inspection Reports
14	(Quality System) Product Identification	Procedures in place to ensure medical gases product identification (labels, colour code) and Product Information Leaflets (if required) comply with national standards.	8.8.1 General; 8.8.6 Cylinder labelling
15	(Quality System) Batch Records	Batch data system defined and key production history data collected by batch number.	7.2.4 Batch Records, 7.5.1 Bulk Manufacture Batch Definition; 7.5.2 Continuous Production Batch Records; 7.5.3 Production Batch Data; 7.5.4 Cylinder Filling Bulk Gas Supply; 7.5.5 Cylinder Filling Batch Record; 7.5.6 Bulk Medicinal Gas Batch Records
16	(Quality System) Document Control	Document control and approval system in place and meet ISO 9000.	7.2.5 Document Control; 7.2.6 Document Approval; 7.2.8 Document Review
17	(Quality System) Record Retention	Local document retention policy and procedures define what and how medical gases data must be kept, and for how long.	7.2.11 Record Retention
18	(Quality System) Non-conforming Product	Any non-conforming products shall be handled in a similar manner to customer complaints (refer to “Customer and Product Recall" elements), i.e., they shall be investigated, the need for product recall determined, and corrective actions identified.	11.2.6 Complaints Review
19	(Production) Quality Control: Responsibilities	QC responsibilities defined but do not have to be independent of production.	5.3.1 Responsibilities; 5.3.2 Independence
20	(Production) Quality Control: Personnel	Personnel are formally responsible for QC and are adequately trained to internal standards.	5.3.4 Person Responsible for Quality Control; 5.3.5 Joint Responsibilities
21	(Production) Processes and Procedures	All medicinal production, filling and gas supply processes are identified, defined and documented (work instructions, procedures, etc).	7.4 Procedures and Work Instructions
22	(Production) Critical Process Areas Identified	Critical processes that impact product specifications are identified, procedures are put in place to reinforce QA and QC for these processes, and all relevant staff are trained in these procedures.	8.2.1 Production Personnel; 8.5.4 In-process Control
23	(Production) Starting Materials Release	Procedure in place for starting material release by staff with QC responsibilities (refer ""Quality Control: Responsibilities")	7.6.4 Release and Rejection Procedures; 8.4.4 Starting Material Release; 8.2.4 Control of Starting Materials
24	(Production) Product Analysis	Analysis frequency and method for verifying compliance of medical gases with specification has been defined and implemented.	9.2.3 Product Release

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	GMP Core Element	Phase I Minimum Standard	AIGA GMP Guide Reference (Doc 023/05)
25	(Production) Product Release	Formal product release by production staff to confirm compliance with specification.	9.2.3 Product Release
26	(Production) Cylinder QC: Pre-fill Checks	Pre-fill checks include test date, visual inspection for damage and cleanliness, and verification that labels, paint and valve outlets are consistent with standards for the product.	8.6.6 Pre-Fill Checks
27	(Production) Cylinder QC: Preparation	Local procedures defined for minimising chance of contamination.	8.6.7 Cylinder Preparation
28	(Production) Cylinder QC: Leak test	Each cylinder filled is leak tested according to defined procedures before release.	8.6.10 Leak Checking
29	(Production) Facilities: Layout and Capacity	Production facilities are laid out in a clear and logical manner and critical medical areas are segregated from other production areas.	6.4.1 Layout; 6.4.2 Segregated Areas
30	(Production) Facilities: Hygiene and Housekeeping	Facilities are maintained in a visually clean and tidy condition, unnecessary materials are minimised, and these are verified by regular inspections.	5.6 Personal Hygiene; 6.2.2 Unauthorised Entry; 6.4.4 Lighting; 6.7.1 Rest Areas; 6.7.2 Toilet Areas; 8.7 Equipment Cleaning
31	(Production) Equipment and Materials: Suitability	Procedures are in place to ensure critical materials and equipment are specified and selected to be "fit for medical purpose".	6.8 Equipment; 6.8.2 Material Selection
32	(Production) Cylinder Package	Product-specific valves, and cylinder package specification and identification conform to national standards	7.3.5 Medicinal Gas Cylinders, 7.3.6 Medicinal Cylinder Valves, 8.6.4 Medicinal Cylinder Valves
33	(Production) Shared Filling System	Medical filling facilities can be shared with non-medical products but only if there are validated methods of preventing backflow into medical products.	6.9.7 Shared Filling Systems
34	(Production) Segregated Storage Area	There are clearly defined and identified segregated areas for "full", "empty" and "quarantine/problem" cylinders.	6.5.1 Layout
35	(Production) Medical Facility Access Restrictions	Basic site security is required. Once on site, access to medical production facilities not necessarily restricted	5.4.2 Visitors; 6.2.2 Unauthorised Entry
36	(Production) Maintenance	Maintenance carried out according to a documented preventative maintenance programme that is specifically designed to minimise hazards to medical product quality.	6.2.1 Maintenance; 6.8.1 Maintenance and Cleaning
37	(Production) Operational Audits	Policies and procedures are in place to ensure planned, regular, specific engineering and operational audits with follow-up.	12.2 Self Inspection Audits; 12.3 Self Inspection Reports

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	GMP Core Element	Phase I Minimum Standard	AIGA GMP Guide Reference (Doc 023/05)
38	(Production) Production Personnel Training	Training needs of all employees involved in medical production and QC identified and up to date; training implemented and results recorded.	5.4 Training
39	(Production) Validation	Quality and production procedures and processes are regularly validated to demonstrate their effectiveness.	8.3.3 Process Validation; 8.3.6 Validation Review
40	(Distribution) Common Bulk Delivery Vehicles	Same truck can be used for medical and other deliveries only if the quality of the non-medical product is at least equal to the medical product, and there are validated backflow protection measures in place.	6.10.3 Common Delivery Vehicles
41	(Distribution) Bulk Storage and Transport	The quality of the gas stored in the storage tank or mobile delivery tanker must be well defined and shall have product-specific couplings.	6.10.1 Storage Tanks, 6.10.2 Common Storage Tanks; 6.10.3 Common Delivery Vehicles
42	(Contract Management and Analysis) Written Contracts	Any manufacture, QC, and supply of medicinal gases from a third party supplier shall be subject to a written contract which specifies compliance to Phase I GMP standards and clearly states the responsibilities of both parties to achieve compliance. (Note: the "Contract Giver" is the receiver of the medicinal gas or starting material covered by the contract, the "Contract Acceptor" is the supplier.)	10.1.1 Principle, 10.2.1 Written Contracts, 10.5 The Contract
43	(Contract Management and Analysis) Responsibilities of Contract Giver (1)	It is the Contract Giver's responsibility to: (i) ensure the Contract Acceptor is able to achieve GMP Phase I standards, (ii) ensure the written contract requires compliance to these standards, and (iii) audit the Contract Acceptor to evaluate compliance.	10.3.1 Responsibilities, 10.5.5 Auditing
44	(Contract Management and Analysis) Responsibilities of Contract Giver (2)	The Contract Giver shall ensure that: (i) all manufactured medicinal gases provided by the Contract Acceptor comply with the provided specifications and Phase I GMP standards, and (ii) the records for contract manufacture, analysis and distribution are retained by, or available to, the Contract Giver.	10.3.3 Product Release, 10.5.4 records
45	(Contract Management and Analysis) Responsibilities of Contract Acceptor (1)	The Contract Acceptor must have suitable premises and equipment, and suitable competent people, to ensure Phase I GMP standards are achieved, and shall give the Contract Giver necessary access to conduct appropriate audits to verify compliance.	10.4, 10.4.1 Contract Acceptor Qualifications, 10.5.5 Auditing

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	GMP Core Element	Phase I Minimum Standard	AIGA GMP Guide Reference (Doc 023/05)
46	(Contract Management and Analysis) Responsibilities of Contract Acceptor (2)	The Contract Acceptor must ensure that all medicinal or bulk gases supplied to them have been manufactured to the agreed specification and GMP Phase I standards, and are suitable for their intended purpose.	10.4.2 Responsibilities
47	(Contract Management and Analysis) Responsibilities of Contract Acceptor (3)	The Contract Acceptor shall not sub-contract any of the manufacture or analysis work without the Contract Giver's approval. If approval is given, the Contract Acceptor shall ensure GMP Phase I standards are maintained. (Note that the Contract Acceptor becomes a "Contract Giver" for the subcontracted work, while the third party becomes a "Contract Acceptor" for that work.)	10.4.3 Sub-contract activities
48	(Contract Management and Analysis) The Contract (Specified Responsibilities)	The contract shall describe clearly who is responsible for: ▪ purchase of raw materials, ▪ testing and release of materials for manufacturing, ▪ production of medicinal gas, ▪ quality control (including in-process controls) sampling and analysis of medicinal gas, and ▪ actions to be taken in the event of the product being identified as out of specification, including corrective actions and product recall.	10.5.3 Specified Responsibilities
49	(Customer and Product Recall) Complaints	There are defined points of contact for medical customer complaints and defined procedures for recording and responding to medical complaints.	11.2.1 Responsibilities; 11.2.2 Written Procedures; 11.2.6 Complaint Review
50	(Customer and Product Recall) Incident and Complaint Investigation	Formal procedure for investigating medical complaints and incidents integrated with recall procedures, and a system for ensuring corrective actions identified and implemented.	11.2.4 Product Review; 11.2.5 Investigation Results; 11.2.6 Complaints Review
51	(Customer and Product Recall) Product Recall Process	Recall responsibilities of management and staff are clearly defined, procedures are written, and relevant employees are trained in these procedures.	11.3.1 General; 11.3.2 Procedure Review
52	(Customer and Product Recall) Identification of Recall Product	The system enables specific batches to be identified, and accurately identifies where potentially affected batches are.	7.6.5 Batch Distribution Records; 11.3.4 Distribution Records

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