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An Overview - International Conference on Harmonisation and ICH (Q1) Stability Testing Guideline for Pharmaceutical Development

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Abstract: The international conference on harmonisations is the invention of three regulatory agency USA, JAPAN, EUROPE. The ICH bringing together with regulatory affair for registration of product and scientific, technical aspect. The mission of the ICH is to improve worldwide harmonization with safety and efficacy also registration and development of high quality with good manner.

The ICH in quality area which provide guidance to conduct stability study, impurity detection, pharmaceutical manufacturing and development, regulatory aspect, good manufacturing practices, quality risk management. The ICH quality guideline control and improve pharmaceuticals drug development with better harmonization.

Keyword: ICH guideline, harmonization, quality guideline, stability studies, GMP.

I. INTRODUCTION

The technical requirement of ich for registration of pharmaceutical products for human use. It is unique in combined with pharmaceuticals industry and regulatory authorities. The international council for harmonisations is changed in international conference on harmonisations. The ICH announces organisational changes it 25 year marks of successful harmonisations.

A. Mission of ICH

To provide better harmonization the interpretation and technical guidance application and requirement for registration of medical products. It also provides registration guidelines for pharmaceutical products.

B. History

The ICH initiation produced in 1980 in Europian community. It is step by step evolved. The Europian community moved towards the development of single marketing guidelines for pharmaceuticals. At the same time the community discussion produced between Japan, USA and Europe. The meeting followed in April 1990 and ICH came into origin.

The International Conference on Harmonisation steering committee was established in meeting since met at least twice in year with location between three regions USA, Europe and Japan. The ICH process was first drawn at the steering committee meeting in Washington March 1992 and amended in Tokyo Sep 1992.

The ICH guidelines on QSEM (Quality, Safety, Efficacy, and Multidisciplinary guideline) the work was also undertaken on important multidisciplinary subject which admitted in medicinal dictionary for regulatory activities (Me DRA) and common technical documents.

C. Objectives of ICH Guidelines

1) to achieve the greater harmonisation in interpretation and applicable technical guidance
2) product registration
3) reduce duplication testing during research and development of new medicine
4) to maintain the aspect between regulatory authorities and pharmactical industry
5) to protection public health from international perspective
6) to update and maintain harmonised technical requirement with greater mutual acceptance of research and development data
7) To provide guidance from manufacturing of new product with GMP compliance.

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D. Membership

The current members and observes as of June 2016, ICH associatio9n comprise the following members and observers:

1) Founding Regulatory Members
a) the Europian commission (EC)
b) the US food and drug administration (FDA)
c) the ministry of health, labour and welfare of japan(MHLW) also represented by the pharmaceuticals and medical devices agency(PMDA)
2) Founding Industry Members
a) (EFPIA) the Europian federation of pharmaceuticals industries and association
b) The japan pharmaceuticals manufactures association (JPMA)
c) The pharmaceuticals research and manufacturing of America (phRMA)
3) Standing Refulatories Members
a) The health Canada
b) The Swiss medic
4) Industry Members
a) (IGBA) the international generic and biosimilar medicines association
b) (WSMI) the world safe- medication industry
5) Standing Observers
a) The international federation of pharmaceuticals manufacturers and association(IFPMA)
b) The world health organisation (WHO)
6) Observers
a) Legistive or administrative authorities
b) The Agencia nacional de vigilancia sanitaria (ANVISA,BRAZIL)
c) The central drug standard control organisation(CDSCO)
d) The commission federal para la protection contra riesgos sanitaria
e) The health sciences authority (HSA, SINGAPORE)
f) The ministry of food and drug safety(MFDS, south Korea)
g) The rozdravnadzor(Russia)
h) The food and drug administration(TFDA, Chinese Taipei)
i) The therapeutic goods administration (TGA, AUSTRALIA)
7) Regional Horomonisation Initatives
a) (APEC) the Asia- pacific economic cooperation
b) (ASEAN) the association of southeast Asian nation
c) (EAC) the east African community
d) (PANDRAH) the pan American network for drug regulatory harmonization
e) (SADC) the southern African development community
8) International Pharmaceutical Industry Organisations
a) The biotechnology innovation organisation (BIO) international organisations with an interest in pharmaceuticals
b) The council for international organisation of medical sciences (CIOMS)
c) The Europian directorate for the quality of medicines and healthcare (EDQM)
d) The international pharmaceuticals excipient council (IPEC)
e) The united states pharmacopeia(USP)

E. Formal ICH Procedure

a) *Consensus Building:* The reporter prepare an initial draft of guideline based on the objective in the objective in the concept paper, and in consolation with expert designated to the EWG. The initial draft and successive revision are circulated for comment interim report are made to each meeting to the ICH steering committee if the consensus is reached within the agreed time table with consensus text with EWG signature is submitted to the steering committee for adaption as step of ICH.

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b) *Start Regulatory Action:* the step is to reached when steering committee agrees, on the basis report from expert working groups that there is sufficient scientific consensus on the technical issue, for the draft guideline to procced to next stages regulatory consolation. This agreement is confirmed by steering committee member.

c) *Regulatory Consolation and Discussion:* at the stage embodying the scientist consensus leaves the ich process to become the subject of normal wide ranging regulatory consolation in the three region. In the EU it is published as a draft CPMP guideline. In the USA it is published as a draft guidance. JAPAN it is translated and issued by MHLW for internal and external consolation.

d) *Adoption of ICH Harmonised Tripartite:* In which the topic return to ICH forum where the starring committee receive a report form the regulatory rapporteur. If both regulatory and industry party are satisfied that the consensus achieved at the step two is not substantially altered as a result of consolation. The text is adopted by steering committee.

e) *Implementation:* having reached step four the tripartite harmonised text moves immediately to final step of the process which is regulatory implementation. This is carried according to same national or regional procedure that applied to other regulatory guidelines and requirement in the EU, JAPAN AND USA.

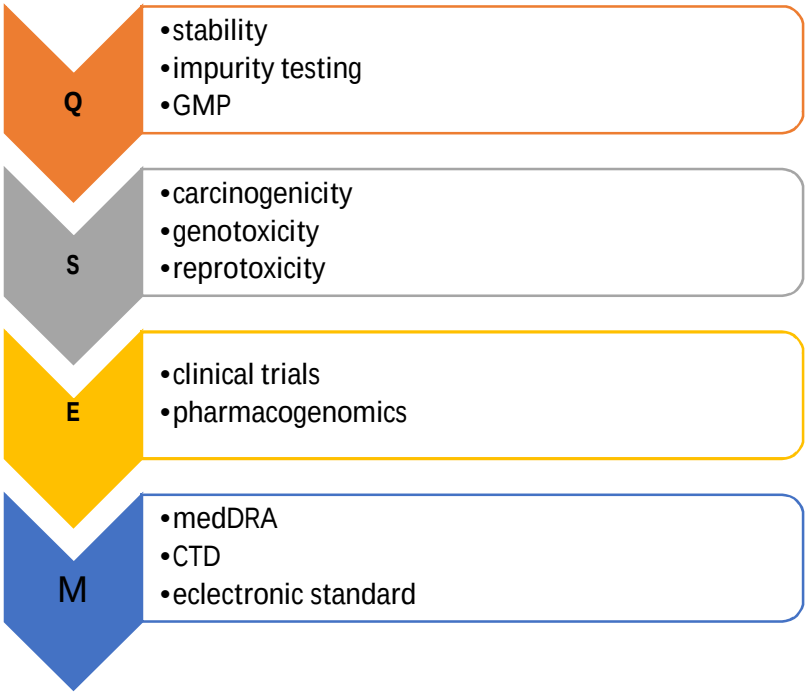
F. *Working Product*

1) ICH guidelines
2) Med DRA
3) CTD
4) Electronic standard
5) Consideration document
6) Open consultation

G. *Benefits of ICH*

1) More than 50 harmonised guidelines
2) Streamline R&D process
3) Rapid access to new medicines
4) Benefits for the regulators
5) Refrences and educational material for non- ICH members

H. *ICH Guidelines*



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I. *Quality Guidelines*

Table 1: Quality Guidelines

Sr.no	guidelines
1	Q1A-Q1F Stability: Q1A: Stability testing of new drug substances and products Q1B: Stability testing: photo stability testing of new drug substances and products Q1C Stability testing for new dosage forms Q1D Bracketing and matrixing designs for stability testing of new drug substances and products Q1E Evaluation of stability data Q1F Stability data package for registration applications in climatic zones III and
2	Q2 Analytical validation: Validation of analytical procedures
3	Q3A-Q3D Impurities: Q3A Impurities in new drug substances Q3B Impurities in new drug products Q3C:Impurities:Guidelines for residual Q3D Guidelines for elemental impunities
4	Q4A-Q4B Pharmacopeia: Q4A: Pharmacopeial Harmonization Q4B Evaluation and recommendation of Pharmacopeial texts for use In the ICH regions
5	Q5A-Q5E Quality of biotechnological products: Q5A Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5B Analysis of expression construct in cells used for production of r-DNA derived protein products Q5C Stability testing of biotechnological/ biological products Q5D Derivation and characterization of cell substrates used for production of biotechnological/ biological products Q5E comparability of biotechnological / biological products subject to changes in their manufacturing process
6	Q6A-Q6B Specifications: Q6A Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6B Test procedures and acceptance criteria for biotechnological/ biological products
7	Q7 Good manufacturing practices for Active pharmaceutical ingredients
8	Q8 Pharmaceutical development
9	Q9 Quality risk management
10	Q10 Pharmaceutical quality system
11	Q11 Development and manufacture of drug substances (Chemical entities and biological entities)

Q1A (R2) Stability Testing Of New Drugs Substances And Products

1) *Objective:* It includes stability data related to drug substances and drug products to register the application for new entity or associated drug in EU, USA, Japan which are three regions of ICH.
2) *Principle:* To provide proof on how the quantity of drug products varies with time under the condition of temperature, humidity, light. The principle says that stability data generated in any one of three regions US, EU, and Japan would be mutually acceptable to other two regions.

To establish period of shelf life of drug products on the basis of stability result. The shelf life is used to decide the expiry date of the each product. To established the retest period for the drug product.

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II. GUIDELINES DRUG SUBSTANCE& DRUG PRODUCT

1. Drug Substance	2. Drug Product
1.1 Stress Testing 1.2 Selection of Batches 1.3 Container Closure System 1.4 Specification 1.5 Testing frequency 1.6 Storage Conditions 1.7 Evaluation 1.8 Statements/Labelling	2.1 General 2.2 Photo stability Testing 2.3 Selection of Batches 2.4 Container Closure System 2.5 Specification 2.6 Testing Frequency 2.7 Storage Conditions 2.8 Evaluation 2.9 Statements/Labelling

A. *Drug Substance*

1) *Stress Testing:* It help identify likely degradation products but only those which are formed under accelerated and long term storage conditions.it establish degradation pathway and establish intrinsic stability of molecule.it validate indicating power of analytical procedure ,depends on individual drug substance and type of drug product ,carried out on a single batch.

Should include effect of

a) Temperature e.g. 50°C, 60°C, 70°C etc.
b) humidity e.g. 75% or greater
c) oxidation
d) hydrolysis across a wide range of pH
e) photo stability as described in ICH Q1B

2) *Selection of Batches*

a) At least three primary batches
b) It manufactured to a minimum of pilot scale
c) With same synthetic route
d) The method of manufacture and procedure should simulate final process
e) The quality representative of quality to be made on production scale

3) *Container Closure System*

The Container closure system same packaging proposed for storage and Distribution of substances.

4) *Specification*

a) *Specification*

i) list of tests,
ii) reference to analytical procedure
iii) proposed acceptance criteria

b) *Test Attributes*

i) attributes that are susceptible to change during
ii) storage
iii) influence quality, safety and/or efficacy
iv) Should cover physical, chemical, biological, microbiological attributes

c) *Analytical Procedures*

i) validated stability indicating
ii) replication depending on results from validation studies

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5) *Testing Frequency*

a) *General:* first year every 3 months, second month every 6 months, than annually proposed re-test period: e.g. 0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months

b) *Accelerated Storage Condition:* 0, 3, 6 months. Where expectation to approach significant change,

c) *Increasing Testing Necessary:* Adding samples at final time point or forth time point in study design: 0, 3, 2 x 6 or 0, 1, 3, 6 months

6) *Storage Condition*

In general case

Study	Storage condition	Study
Long term*	25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%	12 months
Intermediate**	30°C ± 2°C/65% ± 5%	6 months
Accelerated	40°C ± 2°C/75% ± 5%	6 months

Storage in a refrigerator

Study	Storage condition	Minimum time period at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% ± 5%	6 months

Storage in a freezer

Study	Storage condition	Minimum time period at submission
Long term	- 20 °C ± 5°C	12 months

7) *Evaluation*

a) in which min 3 batches of drug substances is tested

b) The degree of variability of individual batch affect the confidence that a future production batch will remain within specification through the assigns re tested period.

c) The analyst must found the batches to batch variability and if it is small than only it is accepted and it can be done by different statistical test.

d) Where the data show so little degradation and so little variability then it is normally unnecessary to go through the statistical analysis, providing a justification for the omission should be sufficient.

8) *Statements/ Labelling:* a storage testing should be established for the labelling based on the stability evaluation of the active substances that cannot tolerate freezing. The term such as ambient condition or room temperature must be avoided.

B. *Stability Testing of Drug Product*

1) *General:* the design of the formal stability studies for the pharmactical product be based on knowledge of the behaviour and properties of the active substances, from stability studies on the active substances.

Design of the formal stability studies should be based on:

a) knowledge and properties of drug substance,

b) Experience gained from clinical formulation studies.

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2) *Photo Stability Testing:* One primary batch, standard conditions according to ICH Q1B
3) *Selection of Batches:* Required are at least three primary batches as:
a) Same formulation and in same container closure system as proposed for marketing.
b) Manufacturing process should simulate that applied to production batches.
c) Same quality and meeting specifications as that intended for marketing. Two of the three batches at least pilot scale third can be smaller for solid oral dosage forms pilot scale is generally on tenth that of full production scale or 100000 tablets or capsules, whichever is larger.

Drug products should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

3) *Container Closure System:* The stability testing should be conducted on the dosage form

Packaged in the container closure system proposed for marketing including any secondary packaging and container label. Supporting information as;

a) Results of open storage of stress testing
b) Studies in other packaging materials

4) *Specification:* Specification is a list of
a) *Test Attributes*
i) Attributes susceptible to change during storage
ii) May influence quality, safety and/or efficacy
iii) It should cover physical, chemical, biological, microbiological attributes.

b) *Analytical Procedures*
i) Fully validated and stability indicating
ii) Replication will depend on results of validation studies

c) *Acceptance Criteria*
i) Based on all available stability information
ii) Differences between release and shelf life acceptance criteria justified
iii) The difference for antimicrobial preservative content supported by validated correlation chemical content and preservative effectiveness
iv) Single primary batch should be tested for antimicrobial preservative effectiveness at proposed shelf life

5) *Testing Frequency*
a) *Long Term Studies*
i) First year every three months. 0, 3, 6, 9, 12
ii) second year every six months: 12, 18, 24
iii) third year and longer annually: 24, 36, 48, 60

b) *Accelerated Studies*
i) General minimum three time points: 0,3,6 months
ii) Expectation of significant change increases testing adding samples at final time point or forth time point: 0, 3, 2x6 or 0, 1, 3, 6 months

c) *Intermediate Storage Condition Studies:* Minimum four time points, including initial and final e.g.: 0, 6,9,12 months, at time of submission 0, 6 months
d) *Reduced Design:* Matrixing or bracketing for reduction of testing frequency if justified

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6) *Storage Condition*

a) *Drug Products in Semi-Permeable Container:* Evaluation for potential water loss for aqueous-based products in semi-permeable containers .Evaluation under condition of low relative humidity.

Study	Storage condition	Minimum time period at submission
Long term	25°C ± 2°C/40% ± 5% or 30°C ± 2°C/35%± 5%	12 months
Intermediate	30°C ± 2°C/35%± 5%	6 months
Accelerated	40°C ± 2°C/not more than 25%	6 months
Accelerated	40°C ± 2°C/75% ± 5%	6 months

Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% ± 5%	6 months

Drug Products Intended Storage in Freezer

Study	Storage condition	Minimum time period at submission
Long term	- 20 °C ± 5°C	12 onths

7) *Evaluation*

a) min 3 batches of drug substances is tested

b) The degree of variability of individual batch affect the confidence that a future production batch will remain within specification through the assigns re tested period.

c) The analyst must found the batches to batch variability and if it is small than only it is accepted and it can be done by different statistical test.

d) Where the data show so little degradation and so little variability then it is normally unnecessary to go through the statistical analysis, providing a justification for the omission should be sufficient.

8) *Statements/Labelling:* a storage testing should be established for the labelling based on the stability evaluation of the active substances that cannot tolerate freezing. The term such as ambient condition or room temperature must be avoided.

C. *Q1b: Photo Stability Testing Of New Drug Substances And Products*

A systematic approach to photo stability testing is recommended covering as appropriate studies such as:

1) Test on active substances
2) Testing on the exposed product outside the immediate pack and if necessary
3) Testing on the product in the immediate pack
4) Testing on the product in the marketed pack

Light Source

a) D65/ID65

b) Standard such as: artificial day light florescent lamp combining visible and ultraviolet output, xenon or metal halide lamp

c) D65 is the internationally recognised standard for outdoor daylight as defined ISO10977(1993)

d) ID65 is the equivalent indoor daylight standard for a light source emitting significant radiation below 320nm, an appropriate filter may be eliminate such radiation.

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D. Q1c: New Dosage Form

A new dosage forms is defined as a medical product which is a different pharmactical product type but containing the same active substances as induced in the existing product approved by the regulatory authority.

1) *It Include:* The product of a different route of admisntration (eg. Immediate release to modified release tablet) and different dosage forms of the same route of administration (eg. Capsule to suspension) . The stability protocol for new dosage forms should follow the guidance in the parent stability guideline in principle .however the reduced stability database at submission time may be acceptable with proper justification.eg. 6 month accelerated and 6 month longer term data from ongoing studies maybe acceptable in certain justified case.
2) *Stability Test Parameter for Various Type of Product*

a) *Tablet:* Appearance. Colour, odour, assay, disintegration/ dissolution, moisture and friability or hardness testing.
b) *Hard Gelatin Capsule:* Appearance, colour, odour of content, assay, disintegration/ dissolution, moisture and microbial limit.
c) *Soft Gelatin Capsule:* Appearance, colour, odour, assay, ph., leakage, microbial limit
d) *Emulsion:* Appearance including phase separation, colour, odour, assay, ph, viscosity, preservative content, weight loss and microbial limit.
e) *Suppositories:* Appearance, colour, odour, assay, particle size, softening range, dissolution and microbial limit.
f) *Small Volume Parenteral drug Injection:* Appearance, colour, odour, assay, ph, preservative, particulate matter, sterility and pyrogenicity.
g) *Large Volume Parenteral:* Appearance, colour, odour, assay, preservative content, particulate matter, sterility and pyrogenicity.
h) *Transdermal:* Appearance, colour, assay, leakage, microbial limit/ sterility, peel and adhesive forces, drug release.

E. Q1d: Bracketing And Matrixing Design For Stability Testing Of New Drug Substance And Product

1) *Bracketing:* it is the design of stability schedule such that only sample on the extremes of certain design factor (eg. Strength, container size,) are tested at all times point in a full design. The design assume that the stability of any intermediate levels is represented by the stability of the extremes tested.
2) *Matrixing:* Matrixing is the design of a stability schedule such that a selected subset of the total number of possible sample for all factor combination would be tested at a specified time point. At a subsequent time point, another subset of sample for all factor combination would be tested. The design assumes that the stability of each subset of sample tested represent the stability of all sample at a given time.
3) *One Half Reduction*

Time point month			0	3	6	9	12	18	24	36
strength	S1	Batch 1	T	T		T	T		T	T
		Batch2	T	T		T	T	T		T
		Batch3	T		T		T	T		T
	S2	Batch1	T	T	T		T		T	T
		Batch2	T				T	T		T
		Batch3	T				T		T	T

4) *One Third Reduction*

Time point(month)			0	3	6	9	12	18	24	36
strength	S1	Batch 1	T	T		T	T		T	T
		Batch2	T	T	T		T	T		T
		Batch3	T		T	T	T	T	T	T
	S2	Batch1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T
		Batch3	T	T	T		T	T		T

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F. Q1e: Evaluation For Stability Data

The parent guideline state that the regression analysis is an appropriate approach to analysing quantitative stability data for retest period or shelf life estimation and recommendation that a statistical test for a batch for pool ability be performed using level of significance of 0.25.

The guideline is intended to provide recommendation on how to use stability data generated in accordance with the principle detailed in the ICH guideline- Q1A(R) stability testing of new substance and product.

1) *Extrapolation:* Extrapolation is the practice of using a known data set to inter information about future data. It is extend the retest period or shelf life beyond the period covered by long term can be proposed in the application, particularly if no significance change is observed at the accelerated condition.

G. Q1F: Stability data Packaging for Registration Application Climatic Zones III and IV

1) A product shelf life should be established according to climatic condition in which the product is to be marketed
2) Storage condition recommendation by manufacturer on the basis of stability studies are meant to guarantee the maintenance of quality, safety, and efficacy through the shelf life of product.
3) Temperature and humidity determine the storage condition and so they greater affect the stability of drug product
4) Climatic condition in countries where the product is to be marketed should be carefully.

The four climatic zone

Climatic Zone	Definition	Storage conditions
I	Temperate climate	21°C/ 45% r.h.
II	Subtropical and Mediterranean climate	25°C/60%r.h.
III	Hot, dry climate	30°C/35%r.h
IV	Hot, humid climate	30°C/70%r.h.

III. CONCLUSION

As the pharmaceutical industry growing globally day by day, there is a great need of developing guidelines those will create harmonization. ICH is formed to develop and implement harmonised guidelines that will reduce the time required for registration of a pharmaceutical product.

ICH guidelines are mainly categorised into four types (Quality, Safety, Efficacy, and Multidisciplinary) which will cover almost all areas required for registration of a pharmaceutical product. The stability should be planned on the basis of pharmaceutical R&D and regulatory requirements.

Forced degradation studies reveal the intrinsic chemical properties of the API, while formal stability studies established the retest date. The variability and time trends of stability data must be evaluated by the manufacturer in order to propose a retest date or expiry date.

IV. ACKNOWLEDGEMENT

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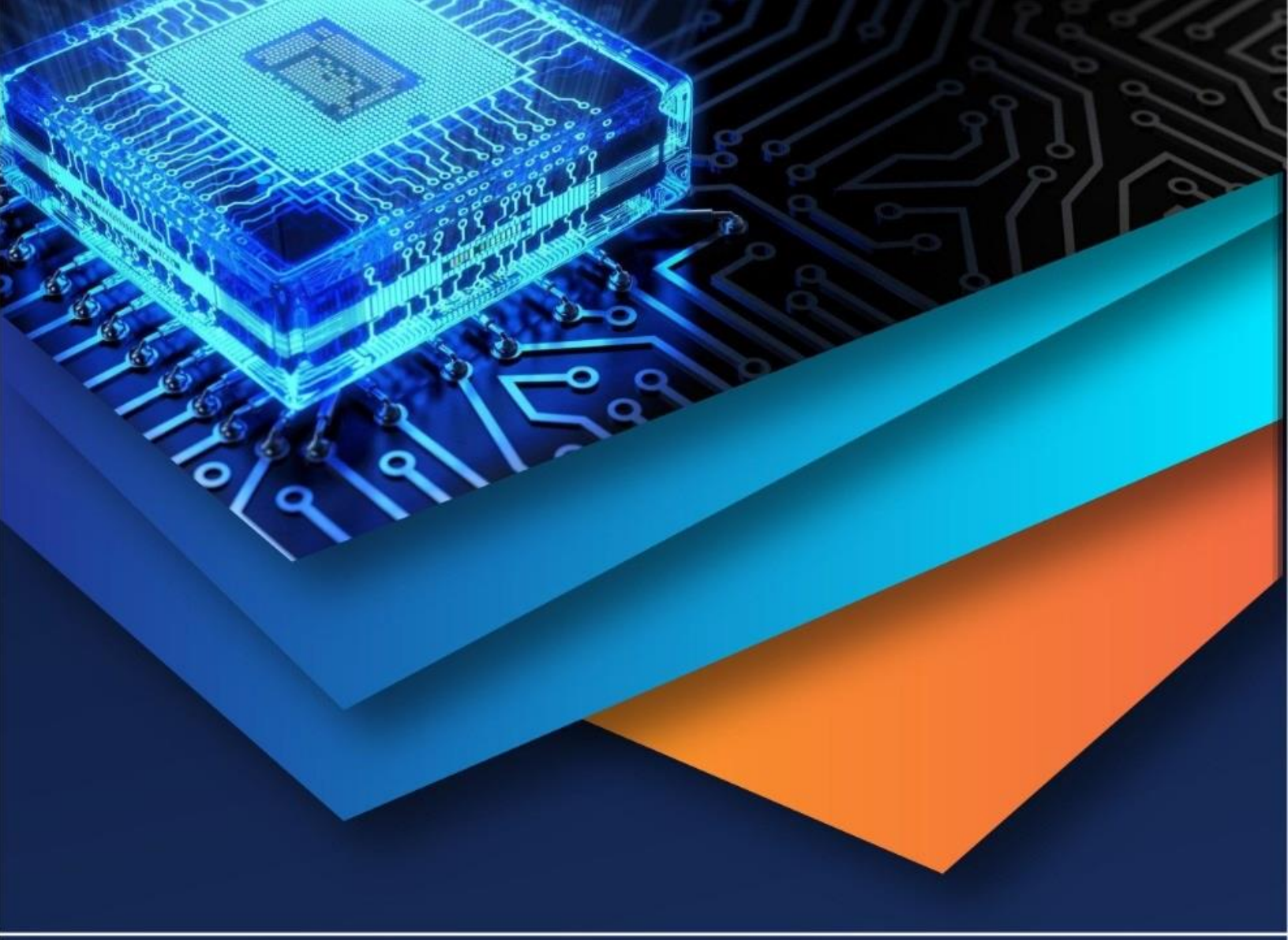

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