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Review Article

## To Study the Regulatory Guidelines for API of Ibuprofen: A Review

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### ABSTRACT

The registration structure of pharmaceutical outcomes is governed by pharmaceutical medication regulatory affairs. It has a broad scope that encompasses all aspects of documentation and marketing in a legitimate format. In our country, the pharmaceutical business is one of the most coordinated industries. Regulatory affairs experts require a current market overview in order to connect pharmaceutical companies with international regulatory bodies. Regulatory issues RA is a career that overlaps a number of industries, including pharmaceuticals, medical devices, and biotechnology. Within the pharmaceutical sector, RA has a specific connotation. DRA is a dynamic field that encompasses both scientific and legal aspects of drug development. DRA professionals are dedicated individuals who take pride in their contribution to improving humanity's health and quality of life. The scope of RA as a profession is much more than the registration of outcomes. They provide strategic and practical advice to businesses at a high level. Their small continues through preparation, marketing, and post-marketing. Professionals from RA help the organisation avoid problems caused by sloppy records, incorrect scientific reasoning, or poor data presentation. The claims that can be made for the product on labelling or in advertising are usually restricted in most outcomes areas where regulatory limitations are imposed.

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### INTRODUCTION:

**R**egulatory affairs is a relatively recent field that arose from governments' aim to protect public health by regulating the safety and efficacy of products in sectors such as pharmaceuticals, veterinary medications, medical devices, pesticides, agrochemicals, cosmetics, and complementary therapies. In the pharmaceutical sector, regulatory affairs can be defined as "the interaction between the Pharmaceutical Corporation and Regulatory Agencies around the world." (1)

Regulatory Affairs is a profession that pertains to the regulation of various industries, such as banking, energy, and pharmaceuticals. It is also very specific to the healthcare industry. This discipline is focused on assessing and communicating the risks and benefits of health care products. It also develops new tools and approaches to improve the safety, efficacy, and quality of regulated products. (3)

Regulatory affairs has moved away from routine and bureaucracy and toward an astonishingly more science- and

issue-based approach. Nowadays, regulatory professionals dedicate a lot of their time to designing experiments and clinical trials that need to be approved, as well as to substantial scientific and medical challenges.

The regulatory department is in charge of offering proactive input and strategic counsel to multinational project teams that are multidisciplinary and involved in product life cycle management. All regulatory facets fall within their purview, such as creating a worldwide regulatory framework, organizing regulatory filings, managing correspondence with regulatory bodies, securing prompt and effective approval, and keeping pharmaceuticals on the market.

Regulatory affairs specialists carry out different tasks during the medication development process based on the company's size and product line.

Securing approval for drug submissions and ensuring that marketed and investigational pharmaceuticals comply with the Food and Drug Act and Regulations are the primary duties of a DRA professional in the pharmaceutical sector. Staying informed about regulatory developments is crucial

for regulatory affairs professionals, since they can impact several aspects of the field such as clinical trials, regulatory strategy, and trial selection.

From pre-marketing development to regulatory filings and the post-approval product life cycles of pharmaceutical products, the regulatory department has a variety of tasks to do.

The regulatory department serves as a hub for information that is sent and received. The regulatory bodies ought to examine a range of information sources, including as published guidelines, speeches given in public, weekly trade publications, casual discussions, and emails. To obtain information, a competent member of the regulatory staff should see, hear, and converse with a regulator, a more seasoned drug development specialist, a colleague, and anybody else who is knowledgeable about regulatory affairs.(2)

#### AIM & OBJECTIVE:

- The primary goal of the regulatory process is to establish a foundation for ensuring high-quality drug goods, which will enhance consumer interest in ensuring efficacy, quality, and safety.
- It also establishes a foundation for future workforce training and qualification.
- To gather and disseminate all necessary statistics and information.
- To study the guidelines of regulatory affairs for the API of Ibuprofen.
- To compare the guidelines of Ibuprofen as per IP, BP, USP.

#### What do regulatory professional ensure in clinical trial-



#### b. Role of regulatory affairs in research and development:

Regulatory affairs professionals collaborate with marketing and research and development to create innovative products that leverage recent advancements in technology and regulations to accelerate time to market. Since new goods are anticipated to significantly boost the bottom lines of the company, even small reductions in time to market translate into significant increases in sales and profit. Adaptive clinical trial techniques, prompt regulatory authority

#### Regulatory Affairs Professionals Responsibilities:

- This person is responsible for keeping track of all the regulatory requirements for a company's products in various regions. They also collect and evaluate the scientific data generated by their colleagues.(4)
- Follow up with the company's product range and current regulations. This ensures that the company's product is compliant with current legislation and customer practices.(5)
- Always maintain relation with legislation, guidelines and customer practices.
- Stay up to date with industries product range. (8)

#### Role of Regulatory Affairs in different Fields:

##### a. Regulatory Affairs in Clinical Trials:

- Clinical trials are center of the drug development & is governed by GCP (Good Clinical Practices) principles and other regulatory guidelines.
- RA is an intermediate between the pharmaceutical industry & health authorities that access safety, quality and efficacy of medicinal product throughout their generation.
- Regulatory Agencies do in the clinical trials –
  - a. Before clinical trials: Review essential documents and give decisions.
  - b. During clinical trials: Perform GCP inspection and end of trials.
  - c. After clinical trials: Assess robustness of evidence and safety all throughout.(6)

approval, and process avoidance can minimize costly errors and delays while hastening the development of new pharmaceuticals.(7)

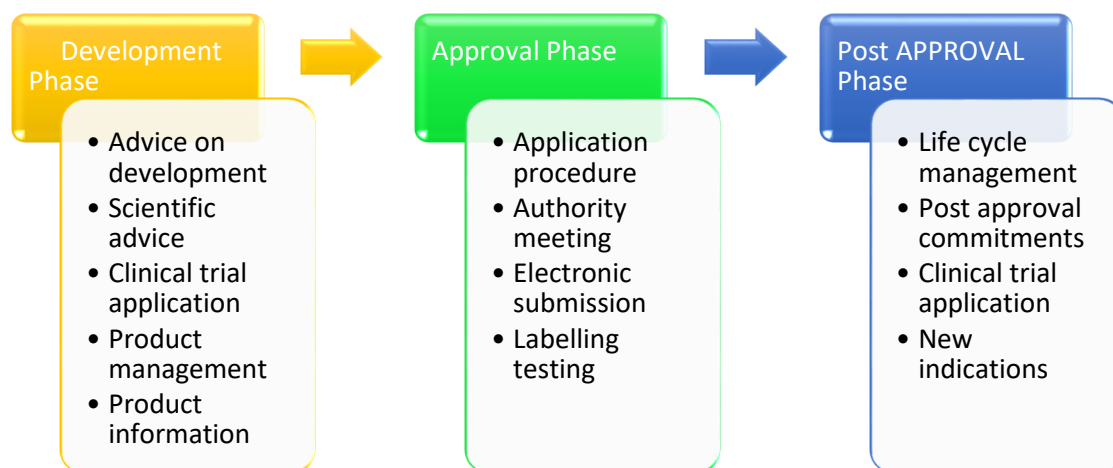
##### c. Role of Regulatory Affairs in Product Management:

A regulatory affairs professional's responsibilities extend beyond simply registering products; they also provide top-level strategic and technical advice to businesses. Their involvement begins with product creation and continues through marketing and post-marketing strategies. Their

guidance at every stage, concerning legal and technical requirements, saves businesses a great deal of time and money when developing and promoting their products. The

World Trade Organization's trade laws between nations and the WHO's guidance on health matters are adopted by governments without their own legislation.(7)

### Product life cycle and regulatory affairs perspective: (11)



### Why RA needs in the pharmacy modules:

India's pharmaceutical sector is growing at a very quick pace, and the country requires more regulatory affairs specialists to meet the demands of the global market.(7) The liaison between regulatory bodies and the pharmaceutical industry is the regulatory affairs professional. According to all applicable laws, rules, standards, and regulatory agency instructions, they must be well qualified. In order to equip pharmacy students with the most recent advancements to carry out tasks in the business, there is an increasing necessity to include the needs of the pharmaceutical sectors into the normal curriculum of pharmacy colleges.(8)

### Regulatory Agencies for Education:

In order to provide students, parents, and employees with an accurate and trustworthy assessment of the many pharmacy colleges around the nation, the Indian government has established a few impartial agencies to evaluate the caliber of the pharmacy profession and categorize the colleges accordingly.

1. The All India Council for Technical Education is the sponsor of the National Board of Accreditation (NBA).

The University Grants Commission's National Assessment and Accreditation Council (NAAC) assessment.(3)

### ICH (International Conference on Harmonization):

ICH is a collaborative effort between European, Japanese, and US regulators and research-based industrial initiatives to explore scientifically and practically the testing techniques needed to assess and guarantee the safety, quality, and effectiveness of pharmaceuticals.(9) The four primary categories of ICH Guidelines are as follows:- ✓ Quality guidelines: Pharmaceutical and chemical quality control.

─ Safety guidelines: Concerning the pre-clinical in vitro and in vivo investigations.

─ Guidelines for efficacy: Concerning human subject clinical trials.

✓ Guidelines for interdisciplinary research: Include issues that don't neatly fall into the aforementioned categories. (9)

### Scope of Regulatory Affairs Professional in Industries:

Regulatory affairs professionals are having chance to employed in industrial sector, government regulatory authorities and academics. Mostly the professionals included in following areas,

- Pharmaceutical
- Medical device
- Diagnostics
- Biologics and biotechnology
- Nutraceuticals
- Cosmetics(3)

### Challenges to regulatory affairs profession:

- Handle the people from diverse background, skills personalities.
- Manage the conflicting loyalties, motivations, ethical, and responsibilities.
- Lead by various regulatory guidance
- Multi-dimensional
- Profuse communication skill
- Collecting income from various department with in the firm about process abilities and product attribute specification.
- Receiving advice from peers about easy way to get approvals.(10)

### Organizational structure of regulatory affairs:

1. Global regulatory affairs.
2. Regional regulatory affairs.
3. Local regulatory affairs.
4. Manufacturing site regulatory affairs.

## 5. Drug agency regulatory affairs.(10)

**Regulatory Strategy:**

- Design of regulatory affairs.
- Arrangement of addressing censorious development issues, which is active and changes during the process.
- Target of how to register a product in the worldwide market (to be in line with corporate, business and strategy of RA unit and projects)

**Major Regulatory Agencies of different countries:**

COUNTRY	REGULATORY AGENCIES
1. India	Central Drugs Standard Control Organization ( CDSCO ) Drug Controller General of India ( DCGI )
2. U.S.	Food & Drug Administration ( U.S. FDA )
3. Australia	Therapeutic Goods Administration ( TGA )
4. Canada	Health Canada.
5. Europe	European Directorate for Quality of Medicines ( EDQM )
6. Brazil	Agencies Nacional de Vigilancia Sanitaria ( ANDVS )
7. South Africa	Medicines Control Council ( MCC )
8. Japan	Japanese Ministry of Health Labor & Welfare ( MHLW )
9. U.K.	Medicines and Health Care Products Regulatory (ANVISA )

- Aim of how to get equivalent time & cost & human resources.(10)

**Reporting of regulatory affairs:**

- Medical director.
- Research and Development director.
- Quality management director.
- Commercial director.
- Managing director or CEO.

**IBUPROFEN:**

A medication called ibuprofen belongs to the non-steroidal anti-inflammatory medicine (NSAID) class and is used to treat inflammation, fever, and pain. This includes rheumatoid arthritis (RA), migraines, and painful menstrual cycles. It can also be used to seal a premature baby's patent ductus arteriosus (PDA). It can be administered intravenously or orally. In about an hour, it begins to function. (12)

For the same conditions as ibuprofen, ibuprofen lysine (commonly known as "ibuprofen lysine") is allowed in some countries; the lysine salt is preferable since it is more water-soluble. (13)

Absorption is significantly quicker since ibuprofen lysine is provided as a lysine salt. However, in terms of the eventual commencement of action and analgesic efficacy, there is no discernible difference between ibuprofen and ibuprofen lysine, according to a Sanai-funded clinical study involving 351 participants in 2020. (14)

In 2006, the Food and Drug Administration granted approval for ibuprofen lysine to close patent ductus arteriosus in premature newborns weighing between 500 and 1,500 g (1 and 3 lb) and under 32 weeks gestation.(15)

**Description:****Name –**

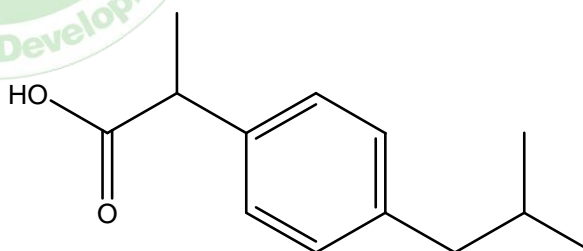
Chemical name of the Ibuprofen is 2-(4-isobutylphenyl) propionic acid, ( $\alpha$ -methyl-4(2-methylpropyl) benzene acetic acid, *p*-isobutyl-hydrotropic acid.

Non-proprietary name of ibuprofen are *race*-ibuprofen

There are various Proprietary names of drug ibuprofen are Advil; Burden; Buffon; Motrin; Unpin; Nurofen. (16)

**Formulae –**

C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

**Structure-**

Ibuprofen

**Molecular weight and CAS Number-**

Molecular Weight = 206.281

CAS = 15687-27-1

**Appearance, Color, Odor-**

Ibuprofen is crystalline in form & color of this drug is white powder and it is odorless.

**Physical properties:****Melting point –**

Ibuprofen typically melts between 75 and 77 degrees Celsius and is a stable crystalline solid. (16)

**Solubility-**



Ibuprofen can be dissolved in a number of non-aqueous solvents. This material dissolves well in alcohols, dimethyl sulfoxide, and chlorinated hydrocarbon solvents. It dissolves sparsely or just partially in nonpolar hydrocarbon solvents.

### Crystallographic Properties:

#### Single Crystal Structure-

Race-ibuprofen crystallizes in the monoclinic space group P21 c, with the following unit cell characteristics, according to an early investigation.

A: 14.667 Å

B: 7.886 Å

C: 10.730 Å

B: 99.362°

Z: 4 molecules per unit cell

In a follow-up work, race-ibuprofen crystals suitable for single crystal X-ray diffraction analysis were isolated from an acetonitrile solution. The following crystal data from this study were also determined, along with the identical monoclinic space group (P21/c):

A: 14.397 Å

B: 7.818 Å

C: 10.506 Å

B: 99.70(3)°

Z: 4 molecules per unit cell

Searching crystallographic databases and performing potential energy calculations were used to conduct a comprehensive assessment of ibuprofen's structural flexibility.

#### Polymorphism-

Apart from its tendency to take on a variety of particle forms. Race-ibuprofen does not seem to exhibit true polymorphism. There are two polymorphic versions of race-ibuprofen's lysine salt, despite the fact that no polymorphs of the drug have been identified. It's important to remember that race-ibuprofen materials can differ in surface areas, stiffness, and/or crystal dislocations across different sources. These alterations affect the compression and granulation processes but have no effect on the melting point. Studies on how ibuprofen crystallinity affects tablet formulation and production have also been conducted. Small crystal lattice variations have been reported in ibuprofen, despite the fact that no polymorphism changes were observed upon compaction. These modifications may have an impact on. (16)

#### Spectroscopy:

##### UV/VIS Spectroscopy –

The UV absorption spectra of race-ibuprofen was obtained in methanol and 0.1 N NaOH. The spectrum is made up of the phenyl ring's weak absorption bands, which are found in the 255-275 nm range and have a molar absorptivity of roughly 250 L/mol cm. The other noteworthy characteristic is the

significantly more intense band system centered at 225 nm, for which the molar absorptivity is almost 9000 L/mol. cm.

##### Vibrational Spectroscopy –

The Kerr pellet was obtained by the infrared absorption spectrum of race-ibuprofen.

##### Nuclear Magnetic Resonance Spectrometry -

###### • <sup>1</sup>H-NMR Spectrum

In deuterated dimethyl sulfoxide, the H-NMR spectra of race-ibuprofen was obtained at a frequency of 400 MHz

###### • <sup>13</sup>C-NMR Spectrum

In deuterated dimethyl sulfoxide, the <sup>13</sup>C-NMR spectra of race-ibuprofen was obtained at a frequency of 100 MHz

##### Mass Spectrometry-

Mass spectrometry number of Ibuprofen is 352144(17)

##### Thermal method of analysis:

##### Melting Behavior

Race-ibuprofen has a melting point between 75 and 77 degrees Celsius, making it a stable crystalline solid. If racibuprofen is allowed to cool to room temperature in a smooth-lined container without vibrating, it can stay in the oil phase for several hours or even days. When the oil phase is disrupted, a bulk crystal emerges vertically from the oil phase, a process known as exothermic recrystallization.

It is important to consider the combination of a low melting point and delayed recrystallization kinetics during the substance's creation since even a small amount of frictional heating during compression could melt the material. Moreover, it has been shown that race-ibuprofen is vulnerable to sublimation; this should be considered when creating production procedures or stability requirements.

It's also important to remember that race-ibuprofen has the ability to form eutectic combinations with a variety of excipients, which can drastically lower the melting point.

##### Differential Scanning Calorimetric -

A single melting endotherm was observed in the sample, with an onset temperature of 74.0°C and a peak maximum of 75.6°C. The sample melted without decomposing, and the melting transition's enthalpy of fusion was determined to be 77.2 J/g.

##### Thermogravimetry –

The weight loss that begins at 100°C cannot be attributed only to thermal decomposition due to the compound's proclivity for sublimation.

##### Methods of Preparation:

A variety of race-ibuprofen synthesis pathways, as well as the separated enantiomers, have been reported. The Boots Pure Drug Company created one of the first industrially viable methods. Al (III) catalyzed acylation of isobutyl benzene results in 4-isobutylacetophenone. The Darken reaction between 4-isobutylacetophenone, sodium

methoxide, and ethyl chloroacetate yields the epoxy ester. Sodium methoxide is hydrolyzed and decarboxylated to make an aldehyde, which is then oxidized to produce racibuprofen with a high yield and purity.

Recently, a three-step catalytic approach that is shorter has been developed. In the last step, a Pad-catalyzed carboxylation procedure introduces the carboxylate group.

### Method of Analysis:

#### Identification-

Ultraviolet Absorption Test, the test solution is produced in 0.1 N Nao at a concentration of 250 g per mile on an anhydrous basis, the absorptivity's at 264 nm and 273 nm do not differ by more than 3.0% from the standard.

The chromatogram of the assay preparation obtained as indicated in the Assay Method shows a significant peak for ibuprofen, with a retention duration (relative to the internal standard) that matches that of the chromatogram of the Standard preparation prepared as recommended in the Assay.

#### Chromatographic Purity:

High-performance liquid chromatography is used to determine the chromatographic purity of the test material. The mobile phase is a suitably filtered combination of acetonitrile and water in a 1340:680 ratio that has been previously adjusted with phosphoric acid to a pH of 2.5.

The test uses an ibuprofen in acetonitrile solution with around 5 milligrams per milliliter. The resolution solution is an acetonitrile-based mixture with approximately 5 mg/mL of ibuprofen and 5 mg/mL of valerophenone. The liquid chromatograph, maintained at  $30 \pm 0.2$  °C, uses a 4-mm x 15-cm column with 5-um packing L1. The detector is set at 214 nm. There is around a two milliliter per minute flow rate.

Chromatograph several 5-μL injections of the test preparation to condition the column. To verify the system's functionality, chromatograph the resolution solution and note the peak responses as shown below.

The following formula determines each impurity's percentage (%Imp),

$$\% \text{Imp} = \{RI / Rat\} 100$$

Where R is the total of all the peaks' responses (not including the solvent peak's), and R is the response of a single peak (aside from the solvent peak and the main ibuprofen peak).

According to the standard, the total amount of all impurities found cannot exceed 1.0 percent, and no more than 0.3 percent of any one contaminant can be recognized.

#### Limit of 4-Isobutylacetophenone:

using the 4-isobutyl acetophenone standard solution prepared in accordance with the Assay instructions and the chromatograms created during the Assay preparation. Using the following formula, determine the percentage of 4-isobutylacetophenone (4-IBAP) in the test material.

$$\% (4\text{-IBAP}) = \{(C/W) (RU / RS)\} 1000$$

Where is the concentration (in mg/mL) of the 4-isobutylacetophenone standard solution? The weight (measured in milligrams) of the test article used to prepare the Assay is represented by W. The ratios of the 4-isobutylacetophenone peak response to the valerophenone peak response obtained from the Standard preparation and the Assay preparation, respectively, are represented by RU and Rest. It is necessary for the detection of no more than 0.1 percent of the sample. (16)

#### Assay:

High-performance liquid chromatography is used to determine the assay value of the test material. 4.0 g of chloroacetic acid are dissolved in 400 mL of water to create the mobile phase, which is then adjusted with ammonium hydroxide to a pH of 3.0. After adding 600 mL of acetonitrile, the mixture is filtered and allowed to degas. The internal standard solution is a mobile phase solution of vandophenone at a concentration of roughly 0.35 mg/ml. A precisely weighed amount of Ibuprofen reference standard is dissolved in the internal standard solution to produce a solution with a known concentration of around 12 mg/mL. A precisely weighed quantity of 4-isobutyl acetophenone should be dissolved in acetonitrile to yield a solution with a known concentration of about in order to create a 4-isobutylacetophenone standard solution around 0.6 mg/ml. In order to prepare a solution containing about 0.012 mg of 4-isobutylacetophenone per milliliter, combine 2.0 milliliters of this stock solution with one hundred milliliters of internal standard solution.

The Assay preparation consists of carefully weighing approximately 1200 mg of the test material, transferring it to a 100-mL volumetric flask, diluting it to volume with internal standard solution, and mixing.

The liquid chromatograph is equipped with a 46-mm x 25-cm column that has packing LI and a 254-nm detector. There is around a 2 mL/min flow rate. To test the system's performance, chromatograph the Standard preparation and note the peak responses as specified under Procedure. The resolution, R, between the ibuprofen and internal standard peaks is not less than 25%, and the relative standard deviation for replicate injections is not more than 2%. The 4-isobutyl acetophenone standard solution should then be chromatographed, as instructed in Procedure, and the peak responses should be noted. Valero phenone and 4isobutylacetophenone have relative retention lengths of roughly 1 0 and 1 2, respectively, and the tailing factors for the different peaks don't go above 25. Additionally, the resolution between the 4sobutylacetophenone peak and the valerophenone peak is not less than 2.5, and the relative standard deviation for replicate injections is not greater than 2.0 percent.

Inject equal amounts (about five for the Standard preparation) into distinct injection tubes to start the Assay Procedure. Using the 4-isobutyl acetophenone standard solution in the chromatograph and the assay preparation, record the chromatograms and measure the responses for the

major peaks. Ibuprofen has a retention time of 10 and the internal standard has a relative retention time of 14.

Using the formula, calculate the amount of analyte (in mg) in a portion of Ibuprofen.

$$\text{Mg IBU} = \{C (R_U/R_S)\} 100$$

where  $R_U$  and  $R_S$  are the peak response ratios found in the Assay and Standard preparations, respectively, and  $C$  is the Ibuprofen standard concentration (in mg/mL) in the Standard preparation.

The specification states that the amount of C<sub>13</sub>H<sub>18</sub>O in USP Ibuprofen must be between 97.0 percent and 103.1 percent on an anhydrous basis.

#### Elemental Analysis:

The calculated elemental percentages for ibuprofen are as follows:

Carbon	75.69%	Hydrogen	8.80%
Oxygen.	15.51%		

#### High Performance Liquid Chromatography (HPLC) Method of analysis:

A number of chromatographic techniques were employed to examine rac-ibuprofen in different pharmacological dosage formulations. Although regular reverse phase HPLC processes are the most commonly used, specific reverse phase HPLC methods have been developed for unique situations.

For instance, an ICMS methodology requires the use of a volatile mobile phase, an ointment for column washing, and a reverse phase ion-pairing HPLC procedure with modified silica gel.

Using a 150 x 4.6 mm Phenomenex C8 reverse phase HPLC column to inject a 0.5 mg/ml sample is one such method that works well with rac-ibuprofen tablets and caplets. This method uses a 55:45 acetonitrile/0.1 M acetic acid mobile phase, which is eluted at a 1.5 mL/min flow rate. The substance's presence is determined by measuring the UV absorbance at 254 nm. The retention period for rac-ibuprofen is roughly five minutes.

For the analysis of rac-ibuprofen solutions, a 15 cm Waters Spherisorb 55C column reverse phase HPLC column is a great option. The mobile phase is 20 mM monobasic potassium phosphate (pH 20) / 44:56 tetrahydrofuran, and the flow rate is 1.0 mL/min. Because THF is utilized in the mobile phase in these HPLC conditions, PEEK tubing cannot be used. Rac-ibuprofen has a retention period of around five minutes, and its detection relies on UV absorbance at a wavelength of 254 nm.

#### Gas Chromatographic method of analysis:

Analytical methods such as gas chromatography can be used. However, this method frequently necessitates derivatization of the analyte prior to injection.

#### Thin –Layer Chromatographic Method of Analysis;

Following the basic method's outline and using silica gel II as the coating ingredient, the British Pharmacopoeia defines

a TLC method to be used during the Identification sequence of testing. 50 mg of the substance to be tested should be dissolved in methylene chloride to create the test solution, which should then be diluted to 10 mL using the same solvent. The ibuprofen reference standard, 50 mg, should be dissolved in methylene chloride and then diluted to 10 ml using the same solvent to create the reference solution.

Five liters of each solution are added to the plate separately to begin the process. To develop the area over a 10 cm route, a mixture of 5:25:75 v/v/v anhydrous acetic acid, ethyl acetate, and hexane is used. The plate is dried at 120 degrees Celsius for 30 minutes. After that, the plate is heated for 20 minutes at 1200C after being lightly sprayed with a 10 g/1 potassium permanganate solution in diluted sulfuric acid. At the end of the process, the plate is examined under 365 nm ultraviolet light.

#### Titrimetric Analysis:

The test value of ibuprofen can also be found using a titration procedure found in the British Pharmacopoeia.

In order to use the method, dissolve 0.450 g of the test material in 50 mL of methanol, then mix in 04 mL of phenolphthalein solution R1. This solution is titrated until it becomes red using a volumetric standard solution of 0.1 M NaOH. A blank titration needs to be carried out in order to adjust the titrant's volume. C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> is comparable to 0.1 M NaOH VS at 20.63 mg/ml.

#### Determination of Body Fluids and Tissues:

The most widely used technology for measuring metabolites and ibuprofen in bodily fluids is high performance liquid chromatography (HPLC). After the entire topic has been looked at

A common sample preparation for HPLC analysis is to add 50 liters of plasma to 150 liters of 95% acetonitrile, which also contains 25 mg/L of internal standard. After 30 seconds of vortexing, the mixture is centrifuged through a microfuge filter for 1 minute, and the supernatant is then injected onto the HPLC.

A number of GC methods based on derivatized ibuprofen have also been developed.

#### Stability.

##### Solid State Stability

When subjected to both ambient and accelerated stability testing, rac-ibuprofen is quite stable in the solid state. After several months of exposure to all of the following environmental conditions, less than 0.1 percent degradation of rac-ibuprofen was detected.

- Ambient temperature and humidity
- Ambient temperature, 100% relative humidity
- 37°C and 60°C, ambient relative humidity.
- 37°C, 100% relative humidity.
- UV light, ambient temperature.

##### Solution-Phase Stability –



Rac-ibuprofen exhibits a high degree of solid state stability when put through both ambient and accelerated stability tests. After being exposed to each of the following environmental conditions for several months, there was less than 0.1 percent degradation of rac-ibuprofen.

Raloxifen has been shown to be comparatively stable in the solution phase, even at harsh conditions like 1 N NaOH, IN HCl, or 50% H<sub>2</sub>O<sub>2</sub>. Two degradants that form in levels less than 0.1% are 2-(4-isobutyrylphenyl) propionic acid and isobutylacetophenone (IBAP).

It is believed that benzylic oxidation and radical-induced decarboxylation lead to the formation of IBAP. To isolate rac-ibuprofen from its degradants, effective HPLC procedures include the USP ibuprofen assay method and the tablet and caplet assay methods.

### Drug Metabolism & Pharmacokinetics:

#### Pharmacokinetics –

Numerous studies have been conducted on the metabolism and pharmacokinetics of rac-ibuprofen and its different enantiomers. Following oral rac-ibuprofen administration, well over 80% of the dosage is absorbed by the GI system (primarily the intestine), and peak plasma levels (t<sub>max</sub>) are reached in 1.5–2 hours. It has been established that eating has no effect on the level of absorption or overall pharmacokinetics of rac-ibuprofen, despite variations in formulation.

Plasma proteins like albumin are associated with over 98% of the rac-ibuprofen present in serum. The apparent half life is thought to be two to three hours long. Comprehensive reports on the rate of absorption and stereochemistry's effect on pharmacokinetics and efficacy can be found in other sources.

#### Metabolism –

The three metabolic routes for rac-ibuprofen include oxidation, acylglucuronide conjugation, and stereochemical inversion of the R-(-)-enantiomer to the S-(+) enantiomer. The primary metabolic process for ibuprofen is oxidation; in humans, this results in the recovery of about 60% of an oral dose in the urine as 2-hydroxy and 3-carboxy-ibuprofen, as well as their glucuronide conjugates.

Numerous pieces of evidence point to the cytochrome P450 family of enzymes as being involved in the hydroxylation of rac-ibuprofen within the oxidative pathway. Less than 10% of an oral intake in humans is accounted for by the second metabolic pathway, direct rac-ibuprofen-glucuronic acid conjugation. This mechanism is moderate.

The process of stereochemical inversion of (R)-ibuprofen in vivo has been studied by numerous researchers. Regardless of the enantiomer that was initially provided, the majority of ibuprofen urine metabolites were found to be of the (S)-configuration, which sparked an initial excitement during experiments conducted in the early 1970s. (16)

### Comparative study of Ibuprofen according to British Pharmacopoeia, United state

#### Pharmacopoeia, and Indian Pharmacopoeia. (18,19,20)

Sr.no	Test	British Pharmacopoeia	United-state Pharmacopoeia	Indian Pharmacopoeia
1.	Identification	A. Infrared absorption spectrophotometry- Comparison ibuprofen with CRS. B. Thin-layer chromatography- Coating the plate with silica gel R.	A. Infrared absorption spectrophotometry- Do not dry specimens.  –	A. Infrared absorption spectrophotometry- Compare the spectrum with that obtained with ibuprofen RS or with the reference spectrum of ibuprofen. B. Thin-layer chromatography- Coating the plate with silica gel H
2.	Content	98.5% to 101.0% (Dried substance)	97.0% to 103.0% (Anhydrous basis)	98.5% to 101.0% (Dried basis)
3.	Storage condition	–	Preserve in tight container.	–
4.	Loss on drying	Maximum 0.5%, determined on 1.000g by drying in <i>vacuo</i> .	Not more than 0.5%	Not more than 0.5% , determined on 1.0g by drying over phosphorus peroxide at a pressure not exceeding 0.1kPa
5.	Sulphated ash	Maximum 0.1%, determined on 1.0g	Not more than 0.5%	Not more than 0.1%
6.	Water	–	Not more than 0.1%	–
7.	Heavy metals	Maximum 10 ppm. 12 ml of solution S complies with test B.	0.002%	2.0g complies with the limit test for heavy metals.
8.	Assay	1 ml of 0.1 M sodium hydroxide is equivalent	–	1ml of 0.1 M sodium hydroxide is equivalent to 0.02063 g of C <sub>13</sub> H <sub>18</sub> O <sub>2</sub> .
		to 20.63 mg of C <sub>13</sub> H <sub>18</sub> O <sub>2</sub>		



9.	Appearance of solution	Solution of 2.0g Methanol R with 20ml solvent is clear and colourless	—	A 10% w/v solution in 95% ethanol is clear and colourless
10.	Optical rotation	+0.05° to -0.05°, determined in a 2.5% w/v solution in methanol.	—	+0.05° to -0.05°, dissolve in 0.50g in methanol R.
11.	Impurity	Impurity F, maximum 0.1%.	Compound C, not more than 0.1% .	Impurity F not more than 0.1% of the principle peak.

## CONCLUSION:

Since the new regulatory perspective is the best model for bringing cutting-edge healthcare support to market quickly and securely, the Regulatory Affairs Profession believes that it will eventually be applied to all healthcare products. The majority of businesses, whether they are tiny, creative biotechnology startups or massive, international pharmaceutical corporations, have specialized regulatory affairs departments. These departments always aim to be the ones least affected by mergers and acquisitions and by economic downturns. Because the resources needed to comply with regulations change, some businesses decide to outsource or outtask regulatory challenges to external service contributors.

Reducing the time it takes for a product to reach the market, and consequently for a company's competitiveness, in today's company's success and growth is critical.

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