Chemical Abstracts Service Registry Number (CASRN or CAS): What's That All About?

When you request an occupational exposure limit (OEL), an acceptable daily exposure (ADE) value, a permitted daily exposure (PDE) value, or occupational health categorization (OHC) determination for an active pharmaceutical ingredient from Provider (Company), we will always ask you for the chemical's CAS registry number (CASRN or just CAS for short), but did you ever wonder, "Why do I need to provide this information with my request?" Or, perhaps, "What is the CAS number and where does it come from?" Or maybe even, "How is it used when there are different forms of the API, like salts?".

What organization assigns CAS numbers?

The Chemical Abstracts Service, a division of the American Chemical Society, assigns unique numerical identifiers to chemical compounds, referred to as a CASRN (Chemical Abstracts Service Registry Number). Information that is collected and organized on the chemical is indexed by The Chemical Abstract Services under the CAS number. According to the Chemical Abstracts Service, the CAS number is a standard used by scientists, industry, and regulatory bodies worldwide as a reliable link between important information and the variable nomenclature that can be used to describe the same compound.

What is the standard format for a CAS number?

While trade, generic, and multiple forms of the formal chemical name can vary, the CAS number precisely defines the molecule of interest and ensures that our work is focused on the correct target. For example, the CAS number for acetylsalicylic acid (aspirin) presents the standard format for CAS numbers. The CAS number for aspirin is 50-78-2: three numbers separated by dashes where the final two are two-digit and one-digit numbers, respectively.

What about different salt forms or hydrates of the same active pharmaceutical ingredient?

Since these are different chemical entities, in addition to the API itself, they also have unique CAS numbers. According to drugs.com, salt forms can include hydrochloride, sodium, calcium, citrate, tartrate, formate, mesylate, etc. If the API is an acid or base, it is most common to find that the salt form is used in therapy. While the biology of these various formulations (API and different salt forms or hydrates) may differ slightly they are often considered to be pharmaceutical equivalents to the parent. Typically, a salt form increases solubility and thereby, the effectiveness of the dose.

Do different salts formulations for the parent API have the same OEL, ADE or PDE?

When the salt formulations of the API are considered equivalent, they also, naturally, have equivalent occupational exposure limits, and acceptable daily exposure (ADE) or permitted daily exposure (PDE) values, which is why you will often see the API and salt forms in the same OEL Monograph.

In 2013, the United States Pharmacopeia (USP) issued a policy entitled, *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* to prescription drug products, which the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) has applied as a guidance for industry. The USP "Salt Policy" states that USP will use the name of the active moiety (the parent), instead of the name of the salt for a drug product when creating drug product monograph titles. The strength of the product is based on the active moiety (the molecule or noncovalent derivative of the molecule responsible for the physiological or pharmacological action of the drug) and contains the salt as an active ingredient but may not include it on the monograph title. The strength of the drug product is expressed in terms of the active moiety and labeling includes an equivalency statement to indicate the amount of the active moiety related to the amount of active ingredient (the salt).

As always, there are exceptions to the idea that all salt forms are equivalent. Discerning when this occurs, and when it is not the case, relies on clinical perspective and requires pharmacological and toxicological expertise. Pharmacokinetic studies may demonstrate that a specific salt form affects absorption, distribution, metabolism,

and/or excretion of the drug in a manner that changes the therapeutic efficacy. For example, as indicated in Patel A, Jones SA, Ferro A, and Patel N (2009), clinically significant amounts of cations such as sodium, potassium, or calcium often used as active ingredients can have an impact on the electrolyte balance in specific patient populations.

Professional and expert interpretation is sometimes required for drug products that do not abide by FDA, EMA, or USP policy and guidelines, or when there is limited information. And, as also indicated in Patel A, Jones SA, Ferro A, and Patel N, in many salt formulations, it is important to understand how adding a low molecular weight counter ion versus a larger counter ion can change the permeability, solubility, duration of action, onset of action, and clearance rate of the active pharmaceutical ingredient. For example, upon review of the literature for dextroamphetamine sulfate and amphetamine, dextroamphetamine sulfate is indicated for the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD) and is a salt form of amphetamine. It is more potent than amphetamine and has a different pharmacokinetic profile, having a different therapeutic effect. Therefore, the occupational exposure limits and health-based exposure limits for dextroamphetamine sulfate and amphetamine are not equivalent and will not have the equivalent toxicological profiles.

Chemical names can also sometimes be confusing. For example, clobetasone butyrate looks like it may be a salt of clobestasone. And the literature often simply calls clobetasone butyrate by the name clobetasone. The story here is, however, quite different as in this case the 'butyrate' is not a salt, but a chemical addition to the clobetasone framework. Colbetasone butyrate has a separate CAS number and is a different, non-equivalent compound compared to colbetasone.

Does Provider (Company) determine if the OEL, ADE or PDE are equivalent for different salt formulations?

You can always count on expert toxicologists here at Provider (Company) to carefully review the available data on the APIs you request, determine salt equivalent formulations when applicable, and include pertinent information when writing OEL monographs, ADE reports, and OHC reports for all of your company's needs.

Reference: Chemical Abstracts Service Registry Number (CASRN or CAS): What's That All About? (affygility.com)