Extracts from regulatory guidelines on use of overages in formulations

European Medicines Agency, 22 June 2017
NOTE FOR GUIDANCE ON PHARMACEUTICAL DEVELOPMENT (EMEA/CHMP/167068/2004)
ICH guideline Q8 (R2) on pharmaceutical development
EMA/CHMP/ICH/167068/2004
Step 5

2.2.2 Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged. Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the

1) amount of overage,

2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and

3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

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The European Agency for the evaluation of medicinal products
Human medicines evaluation unit
Note for guidance on Development Pharmaceutics CPMP/QWP/155/96

3.1 Overages

The use of overages in the formulation of medicinal products is a practice which in general terms needs to be discouraged because of the risk of overdosing.
Overages are primarily employed to cover losses during manufacture of active substances or key excipients, i.e. manufacturing overages and/or during shelf-life i.e. stability overage. These can be distinguished since in the former case there is unlikely to be increased dosage administered to the patient, whereas the stability overage will result in overdosing where batches of products may read the patient soon after release. The inclusion of any overage should be justified. Large overages (for example in excess of 10%) should not normally be used to cover up inherently unstable formulations. It is better to reduce a shelf life rather than to risk exposing a patient to excessive doses of a drug. Similarly, overages should not be used to cover up imprecise or inaccurate analytical test procedures or sub-optimal manufacturing processes. The introduction of an overage of an active substance into a formulation should always be justified on the grounds of safety and efficacy of the product. It should also be remembered that over dosage may be introduced by the mechanism of delivery, e.g deposition of a metered-dose inhaled drug in the mouth.

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ICH Q8: Pharmaceutical Development. Regulatory Requirements Directed by the New Note for Guidance (EMEA/CHMP/167068/2004) in Comparison to the Previous Guideline (CPMP/QWP/155/96). A Critical View from the Generic Pharmaceutical Industry.

2.2.2 Overages (3.2.P.2.2.2) Overages of the drug substance compensating for degradation during the manufacture or shelf life are generally discouraged by authorities since these can negatively influence the safety and efficacy of the product. If an overage of the formulation is used, any information about the amount and reason of the overage and the justification for the amount of overage should be provided. The overage should be fully included in the batch formula (3.2.P.3.2).

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WHO Expert Committee on Specifications for Pharmaceutical Preparations
Forty-sixth report
Annex 3
Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

Overages 3.2.P.2.2.2
Any overages in the formulation(s) described in 3.2.P.1 should be justified. Justification of an overage to compensate for loss during manufacture should usually be provided in the PD, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).
Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

Guidance for Industry Drug Stability Guidelines - U.S. Department of Health and Human Services Food and Drug Administration Centre for Veterinary Medicine (CVM) December 9, *Remington's Pharmaceutical Sciences, Sixteenth Edition, Pg. 284 (1985)*2008
The active ingredient should be formulated in any drug preparation at 100% of label claim. An overage of the active ingredient may be permitted in a product should the need exist. All overages should be justified. The assay limits must account for the overage. The overage should not exceed the limits of 5% for antibiotics and 3% for non antibiotic chemicals as established by the Centre for Veterinary Medicine.

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TGA
4. Development pharmaceutics and formulation
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Information which is relevant to the subheadings specified in the CTD under module 3.2.P.2 should be included in this section. For example, explanations for the choice of excipients, the use of a modified release dosage form, or justifications for overages. For most OTC medicines this section will be brief.

4.1 Overages and ranges

Details should be provided of any overage or range that is applied during manufacture, including a justification for the overage or range and supporting validation data where appropriate.
Any assay limits which are unusually wide as a consequence of the proposed overage should also be addressed. Refer to 'Section 7 Control of finished product', for examples of some commonly applied assay limits. Overages are not to be included in the formulation details section of the electronic application form.
Justifications for 'stability' overages would generally include comment on:

- the intrinsic stability of the active substance, and any studies performed to investigate and/or control its stability in the product
- any implications for safety or efficacy of the product, as a consequence of the wide range of the ingredient's content over the shelf life of the product
- any implications for safety of the product resulting from the presence of any degradants.

For some substances the weight used in a batch may vary according to its moisture content or according to its potency. Variation of the quantity of active substance, to adjust for potency, may affect the proportions of excipients present in the finished product relative to the nominal formula. In some situations, the manufacturer may opt to compensate for the fluctuations in the weight of raw material by adjusting the amount of a nominated excipient in order to maintain a target weight for the batch. In this case, the following information should be provided regarding the proposed range in quantity:

- estimated potency and/or water content
- a formula showing how the amount of adjustment will be calculated
- an indication of which other excipients will be varied correspondingly, if any, and within what limits

Validation data may be necessary to support a wide range. Such validation data can be generated using 'side batches' (small scale batches or modified portions of production batches) with the formulation or properties (e.g. pH) at the extremes of the proposed range. Validation data may include:

- compliance with the finished product specifications
- stability data
- in some circumstances, comparative dissolution profiles may also be appropriate.

3.2.P.3. Manufacture [{Drug Product Name}, {Dosage Form}]

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

Table 1: Batch Formula Table

Core Tablet		
Component	**Quality Standard**	**Amount (kg) per batch**
Drug Substance	In House Standard	500
Excipient X	USP/NF	310
Excipient Y	USP/NF	280
Excipient Z	In-House Standard	50
Magnesium Stearate	NF	15 (range 14.5 to 15.5)
Purified Water	USP	(200)[a]
Total Batch Size		X
Film Coat Solution [b]		
Hydroxy Methylcellulose	USP	10
Purified Water	USP	(200) [b]
Color Red	DMF Holder Y Standard	10
Color White	DMF Holder Z Standard	1.5
Total Batch Size		Y
Print Ink Solution		
Colorant		0.15
Solvent		10
Total Batch Size		Z

[a] Water is removed during processing

[b] Film coat weight variability is 80 - 120% or target

Overages in Dietary Supplements

General Notices statement:

- An official product shall be formulated with the intent to provide 100% of the quantity of each ingredient declared on the label. Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper acceptance criterion contained in the monograph may be increased by a corresponding amount.
- Typical acceptance criteria in USP monographs are symmetrical with respect to 100% considering the analytical variation of the assay procedure and unavoidable variations in manufacturing process.
- Where analytical variation was very high, asymmetric limits for assay/strength were included in monographs (microbial/biological assays)
- Formulations should be developed to achieve stability
- Compensation of loses of nutrients over time should be used as the last resort and limited to products where toxicity due to vitamin overdose is not a safety concern (not at high doses of vitamin A and D)

Overages vs Monograph Specifications

Overage in Master Formulas not the same as release specifications

- Loses during manufacturing process should be included

Monographs were developed over a long period

Evolution of Analytical technology (Microbial Assays, animal assays vs UPLC)

Manufacturing process improvements, stabilization strategies (vitamin coatings, beadlets, separation of incompatible substances, antioxidants, photosensitivity, pH control, etc.)

To determine the overage to achieve a 100% at a prefixed expiration date!

Unstable formulations will contain at expiration date an amount of degradation products equal to the overage added to the formulation.

Do you know the toxicity of those degradation products? Responsible companies should educate retailers about the need for shorter expiration dates in certain dietary supplements (gummies).

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In qualitative-quantitive batch formula if any Overages to be added, it can be tabulated as below:

#	Component	Quality Standard	Function	Qty/ tablet (mg)	Qty/ batch (kg)	Any overages in (% and mg)	Overages qty/ tablet (mg)	Overages qty/ batch (kg)	Final quantity per batch (kg)
	Drug Substance								
	Excipient X								
	Excipient Y								
	Excipient Z								

Justification:

Calculation:

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