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Professional paper

Advantages of trend analysis in stability studies for prediction of potential OOS result within estimated shelf-life of medicinal product

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Abstract

Stability studies are crucial for pharmaceutical product registration, providing vital data to assess batch-to-batch consistency, monitor critical quality attributes, and ensure the product's quality, safety, and efficacy over its entire shelf life.

Identifying potential issues such as potential out-of-specification (OOS) results and ensuring data quality is often facilitated by employing objective methods for trend analysis of stability data.

The goal of the research was to explore the advantages of trend analysis in stability studies, highlighting its significance in forecasting OOS results and ensuring the consistent performance of pharmaceutical products within their estimated shelf life.

To evaluate stability data and find the pattern of data that indicates change over time, stability studies for Lisinopril/Amlodipine tablets 20mg/10mg were subjected to trending analysis based on data from annual or routine stability studies. The trending analysis was performed to evaluate whether the data demonstrates increasing or decreasing trend (change of mean) for the stability indicating parameters over time or the data indicate no discernible change at all, as well as predicting potential OOS results during shelf life. Regression analysis as a statistical tool for trending analysis, is considered an appropriate approach to evaluating the stability data for a quantitative attribute.

Key words: stability studies, evaluation of stability data, long term stability, lisinopril, amlodipine, tablets.

Introduction

In the pharmaceutical industry, ensuring the quality, safety, and efficacy of fixed combination medicinal products throughout their shelf life is of paramount importance. Stability studies play a crucial role in this process, providing essential data that support regulatory decisions and product formulations (ICH Q1A, 2003). These studies yield vital stability data that is crucial for evaluating variations in key quality attributes and ensuring consistency across different batches for effective quality control (ICH Q1A, 2003).

Stability studies are carried out on an annual basis to support modifications in products or processes, ensuring ongoing quality in production batches. One of the key methodologies employed in these studies is trend analysis, which systematically examines stability data over time to identify patterns and predict potential out-of-specification (OOS) results, thus preventing the release of a product not

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meeting its intended shelf-life requirements, potentially impacting patient safety and regulatory compliance (FDA Guidance, 2003) by leveraging trend analysis, manufacturers can proactively detect deviations, optimize product formulations, and enhance quality control measures.

The detection of potential issues, including OOS results, and the maintenance of data integrity are typically improved by employing objective methods for analyzing trends in stability data. The analysis of stability data following the assessment of shelf life should focus on the trends and variability present in long-term stability data. The objective of trend analysis in stability studies is to detect unusual trends and potential OOS results over the long term, while also leveraging trending data to accurately predict the product's shelf life and make any necessary adjustments to labeling.

Using advanced statistical methods, such as regression control chart method for trend analysis versus basic statistics, could predict the likelihood and therefore to prevent occurrence of potential OOS results with increased accuracy.

Regression control chart method can be used to monitor processes over time, make predictions, and identify trends based on statistical relationships instead of straightforward overview of stability data using descriptive statistic and tabular presentation of data.

According to ICH Q1E guideline, evaluation of the stability data, after the assessment of the shelf life, should progress through the trends and variability of the long-term stability data. Non-compliance with regulatory requirements related to OOS situations can result in regulatory actions, product recalls, fines, or legal consequences for the responsible entities.

There has been much discussion on how to identify, document and investigate out-of-specification (OOS) results in pharmaceutical development and manufacturing (ICH 2005; FDA 2006), but so far, there is no clear regulatory guidance on how to detect and handle the OOT results. An atypical trend or an outlying result may indicate an increasing likelihood of future OOS results. A review of recent Establishment Inspection Reports (EIRs), FDA Form 483s, and FDA Warning Letters indicates the identification of OOT data is becoming a regulatory issue for marketed products. It is important to distinguish between OOS and OOT results. FDA issued an OOS guidance and much has been written in the scientific literature and discussed at many scientific conferences about OOS results. Although the FDA guidance indicates in a footnote that much of the guidance presented for OOS can be used to examine out-of-trend (OOT) results, there is no clearly established legal or regulatory basis to require consideration of data within specification but not following expected trends.

There is a necessity for effective and practical statistical methods to analyze stability data trends in order to identify when a batch or result deviates from expected behavior. To determine if a specific result is out-of-trend (OOT), we first establish the expected outcomes and identify the relevant data comparisons. Two general approaches can be employed to trend the data.

The first approach is to look across historical stability batches to determine whether the result/data is following the same trend as other batches of the same product. The second is to look within a batch to determine whether that batch is following the same trend across time as indicated by data for earlier time points. Because observations from several time points are needed to establish a trend, this approach could only be used adequately for later time points. The statistical tool that can be used for these two situations is regression control chart method. Currently, no common agreement exists about which of these situations should be considered or whether both are equally important.

The goal of the research was to explores the advantages of trend analysis in stability studies, highlighting its significance in forecasting OOS results and ensuring the consistent performance of pharmaceutical products within their estimated shelf life.

Material and methods

Lisinopril/Amlodipine tablets 20mg/10mg is a pharmaceutical product with long manufacturing history. Once started manufacturing, it respectively follows the same manufacturing route, on the same manufacturing site and following described manufacturing procedure in Alkaloid AD Skopje. This product has well-established stability and was chosen as a suitable candidate that would be subjected to trending analysis of the parameters appearance, color, assay, dissolution rate, related and degradation products and microbiological purity regarding their specification limits.

Ongoing stability studies in Alkaloid AD Skopje are performed on one batch annually for long term stability testing on commercial batches on storage conditions temperature 25±2 °C and relative humidity 60±5%, including the batches produced in four consecutive years.

- Lisinopril/Amlodipine tablets 20mg/10mg batch 1
- Lisinopril/Amlodipine tablets 20mg/10mg batch 2
- Lisinopril/Amlodipine tablets 20mg/10mg batch 3
- Lisinopril/Amlodipine tablets 20mg/10mg batch 4

The batches subject to stability study are manufactured, packed, and tested in Alkaloid AD Skopje.

In order to evaluate trends and variability of the long-term stability data, the following critical quality parameters (CPQs) were evaluated:

- dissolution rate and microbiological purity, using basic statistics, such as descriptive statistics and tabular and graphical presentation of data.
- assay and related and degradation products, using statistical method: regression control chart method.

Minitab Statistical software was used for the

evaluation by regression control chart method. This software is a powerful statistical software used for regression analysis and other data analysis tasks that can look at current and past data to discover trends, find and predict patterns, uncover hidden relationships between variables, and create visualizations to tackle even the most daunting challenges and opportunities.

Results and discussion

For the purpose of this research, a product with well-established stability Lisinopril/Amlodipine tablets 20mg/10mg was chosen for evaluation of trending analysis of the selected parameters considered critical: appearance, color, assay, dissolution rate, related and degradation products and microbiological purity regarding their specification limits using the most recently introduced analytical method. The stability data was assessed in order to identify patterns that signify changes over time within estimated shelf-life of fixed combination medicinal product. The trend analysis was conducted to evaluate whether the data reflected an increasing or decreasing trend (change in mean) for the stability-indicating parameters over time, or if it indicated no notable changes, as well as to anticipate potential out-of-specification (OOS) results throughout the shelf life. Thus, all collected stability data obtained for these parameters through the years were evaluated.

For the time being, and due to absence of clear regulatory guidance, we use advanced statistical methods (regression control chart method) only for establishing the trend of stability data for the parameters: assay and related and degradation products as CQAs. To statistically evaluate the trend and variability of the long-term stability data for the parameters dissolution rate, and microbiological purity, basic statistical methods such as descriptive statistics and tabular and graphical data presentations were employed.

Appearance and color

Parameters such as appearance and color are not trended since the results for these parameters are not numerical. The results align with the specification requirements for the examined timelines of 0, 3, 6, 9, 12, 18, 24 and 36 months.

Assay of lisinopril and amlodipine

In order to statistically evaluate the trend and the variability of the long-term stability data for the parameter assay of the active ingredients we used a regression control chart method from data among batches. For comparison among batches, a regression line is fit to the historical database for the product assuming a common slope but allowing for various batch intercepts. This fit will provide an estimate of the intercept, the slope, and the square root of the mean square error from historical data. According this statistical tool, parameter Assay will be trended on the following testing frequencies: 0, 3, 6, 9, 12, 18, 24 and 36 months. Stability data for parameter assay is given in Table 1. Trending analysis is presented in Figure 1 and Figure 3, respectively for amlodipine assay and lisinopril assay. Regression analysis (Response versus Frequency) for amlodipine assay and lisinopril is graphical presented in Figure 2 and Figure 4, respectively.

From the presented data (Table 1 and Figure 1) and regression analysis presented in Figure 2 (an estimate of the expected result at any given time point for a given batch specified by the following relation: Response = 99.49 + 0.045 * Frequency), we can see that results within all batches are resulting in no discernible change over time. Results for this investigated parameter remain within the specification requirements without potential OOS result during shelf life.

Table 1. Stability data for the parameter assay of active pharmaceutical ingredients (lisinopril and amlodipine) in Lisinopril/Amlodipine tablets 20mg/10mg

Frequency (months) / batch	0	*3*	*6*	*9*	*12*	*18*	*24*	*36*
Parameter: Lisinopril assay								
batch 1	101.72	100.50	100.60	99.37	100.76	99.92	100.92	101.26
batch 2	100.16	98.24	99.58	99.90	100.24	101.07	100.86	
batch 3	100.08	98.68	98.59	98.71	99.64	100.05		
batch 4	98.18	99.78	100.42	100.28	98.92			
Parameter: Amlodipine assay								
batch 1	100.51	98.76	99.70	97.25	98.38	98.54	96.59	100.98
batch 2	100.27	99.65	98.78	99.06	99.28	99.35	99.65	
batch 3	99.71	98.77	98.99	98.93	101.43	100.34		
batch 4	98.14	99.05	99.87	100.02	99.10			

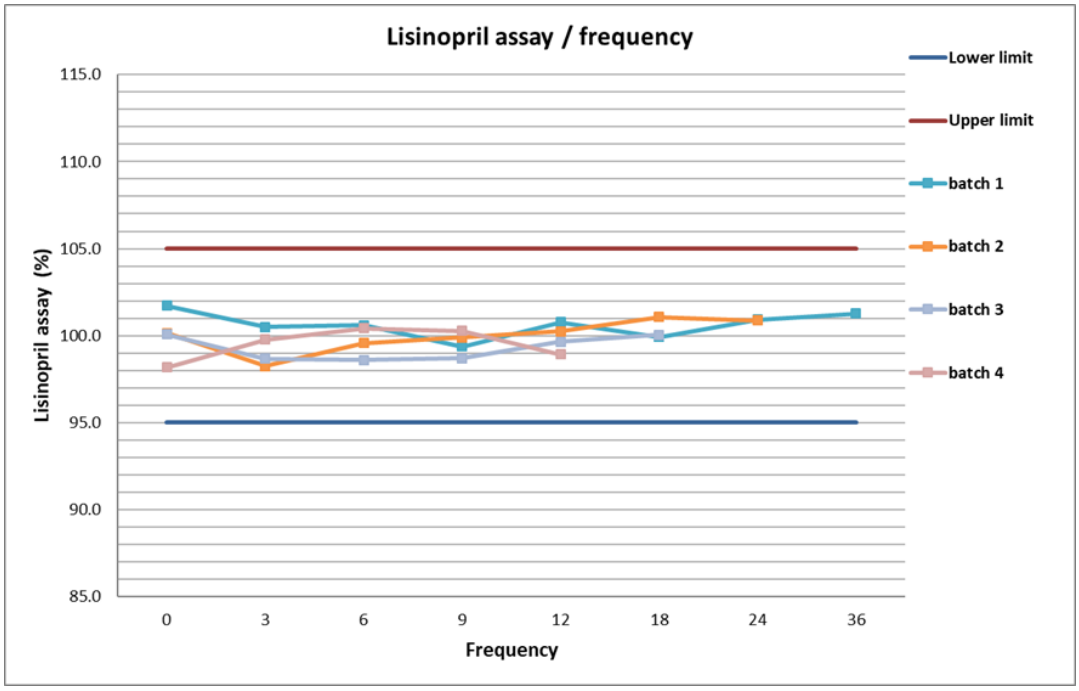

Fig. 1. Trending analysis of Lisinopril assay

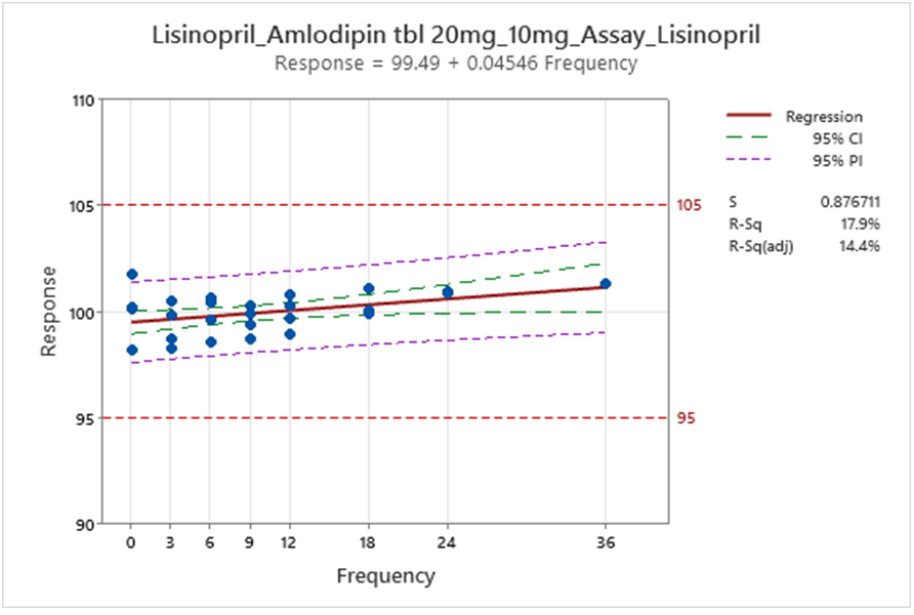

Fig. 2. Regression analysis: Response versus Frequency for Lisinopril assay.

From the presented data (Table 1 and Figure 3), and regression analysis presented in Figure 4 (an estimate of the expected result at any given time point for a given batch specified by the following relation: Response = 99.23 + 0.005 * Frequency), we can see that results within all batches are resulting in no discernible change over time. Results for this investigated parameter remain within the specification requirements without potential OOS result during shelf life.

Dissolution rate of lisinopril and amlodipine

For the dissolution rate for lisinopril and amlodipine, the data indicates no discernible change over time. All results meeting shelf-life requirements. Tabular analysis of the parameter dissolution rate of lisinopril and amlodipine is given in Table 2, and graphical presentation is given in Figure 5 and Figure 6 respectively for amlodipine and lisinopril dissolution rate.

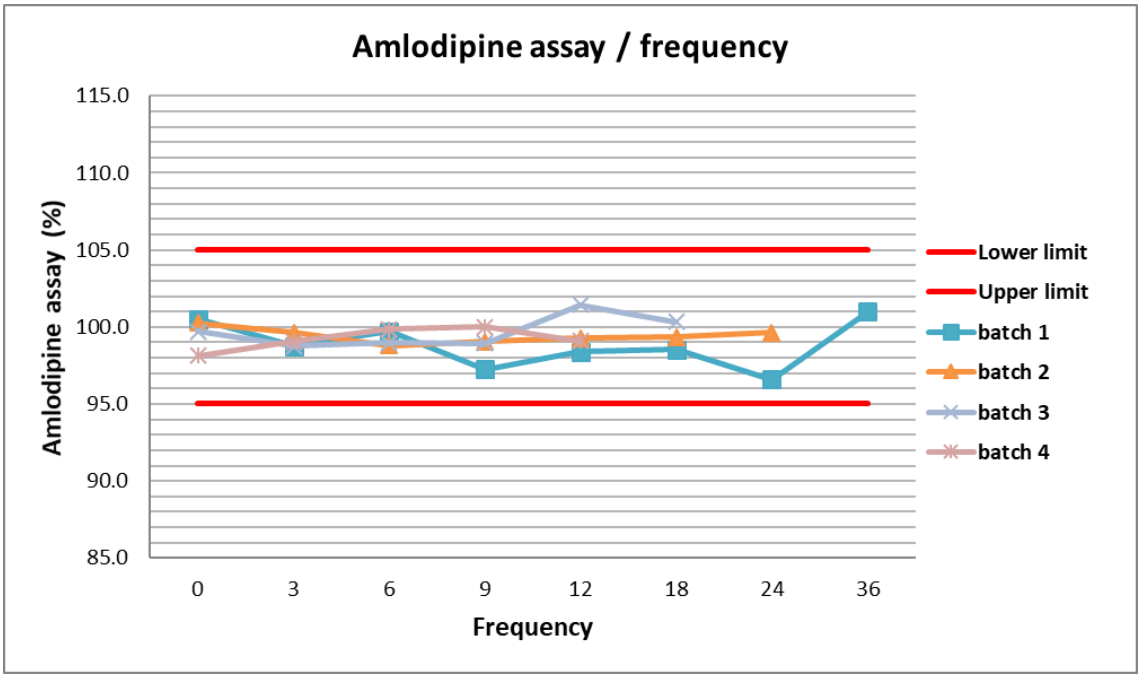

Fig. 3. Trending analysis of Amlodipine assay.

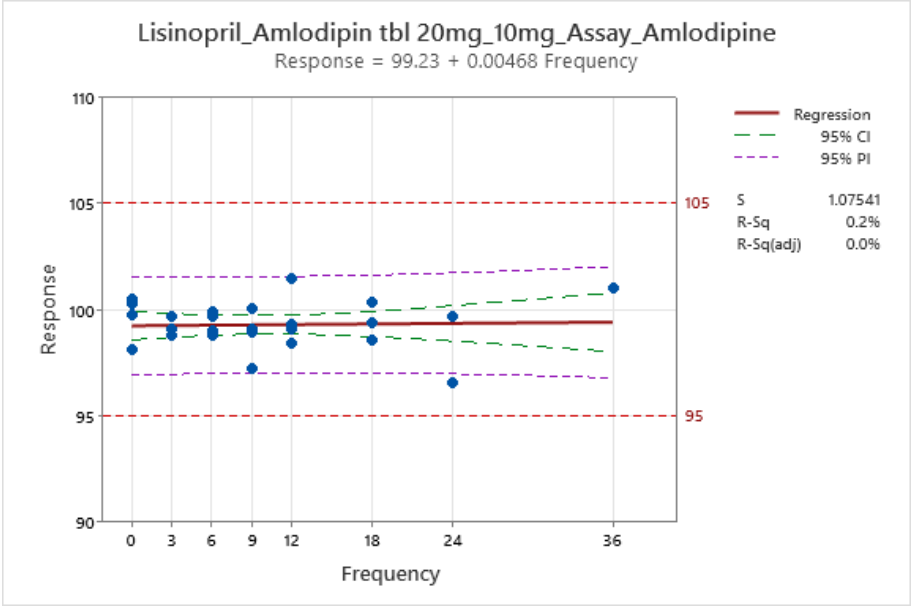

Fig. 4. Regression analysis: Response versus Frequency for Amlodipine assay.

Related and degradation products

Results for this investigated parameter comprises two sets of related and degradation products originating from both active pharmaceutical ingredients.

The results for specification parameter related and degradation compounds from lisinopril (that include: impurity C, any unspecified impurity and total impurities) are given in Table 3 and Figure 7.

The results for specification parameter related and degradation compounds from Amlodipine (that include: Impurity D, Impurity F, any unspecified impurity and total impurities) are given in Table 4 and Figure 8.

All collected data for the related and degradation compound from lisinopril (Impurity C, any unspecified impurity and total impurities content) indicate no discernible change**.** All the results within a batch remain almost constant around the initial result value (excluding the possible analytical error during performing the analysis). The scope of the adverse trend does not fall out the specification limits. An estimate of the expected result

at any given time point for a given batch is specified by the following relations:

- For impurity C: Response = -0.01 + 0.002 * Frequency
- For any unspecified impurity: Response = 0.08 + 0.000 * Frequency
- For total impurities: Response = 0.13 + 0.002 * Frequency

Only for impurity C, we can see that results within a batch 1 are resulting in adverse trend compared to the other batches. This situation where adverse trend has been identified is monitored closely. We identified that batch 1 has been initiated routinely, as ordinary typical batch, without deviation and change control.

Results for this investigated parameter remain within the specification requirements without potential OOS result during shelf life.

For all collected data for the related and degradation compound from Amlodipine (Impurity D, Impurity F, any unspecified impurity and total impurities content) we find that they indicate no discernible change**.** All the results within a batch remain almost constant around the initial result value (excluding the possible analytical error during performing the analysis). For the Impurity F content, we can see that results within a batch 2 are resulting in adverse trend compared to the other batches. This situation where adverse trend has been identified is monitored closely. We identified that batch 2 has been initiated routinely, as ordinary typical batch, without deviation and change control. The scope of the adverse trend does not fall out the specification limits.

Table 2. Trending analysis of the parameter dissolution rate of active pharmaceutical ingredients (lisinopril and amlodipine) in Lisinopril/Amlodipine tablets 20mg/10mg

Frequency (months) / batch	0	*3*	*6*	*9*	*12*	*18*	*24*	*36*
Lisinopril dissolution rate								
batch 1	99.56	98.06	97.09	95.99	97.52	98.16	98.68	99.22
batch 2	98.59	97.55	94.57	95.52	98.94	99.39	98.30	
batch 3	97.50	96.33	93.45	95.69	98.10	96.25		
batch 4	98.17	95.12	95.79	92.58	99.05			
Amlodipine dissolution rate								
batch 1	96.20	90.73	90.56	91.14	92.28	91.49	94.81	93.68
batch 2	97.02	91.76	90.62	91.10	93.48	95.10	93.58	
batch 3	92.00	92.63	92.41	91.42	95.58	93.16		
batch 4	93.41	93.50	91.37	89.77	94.97			

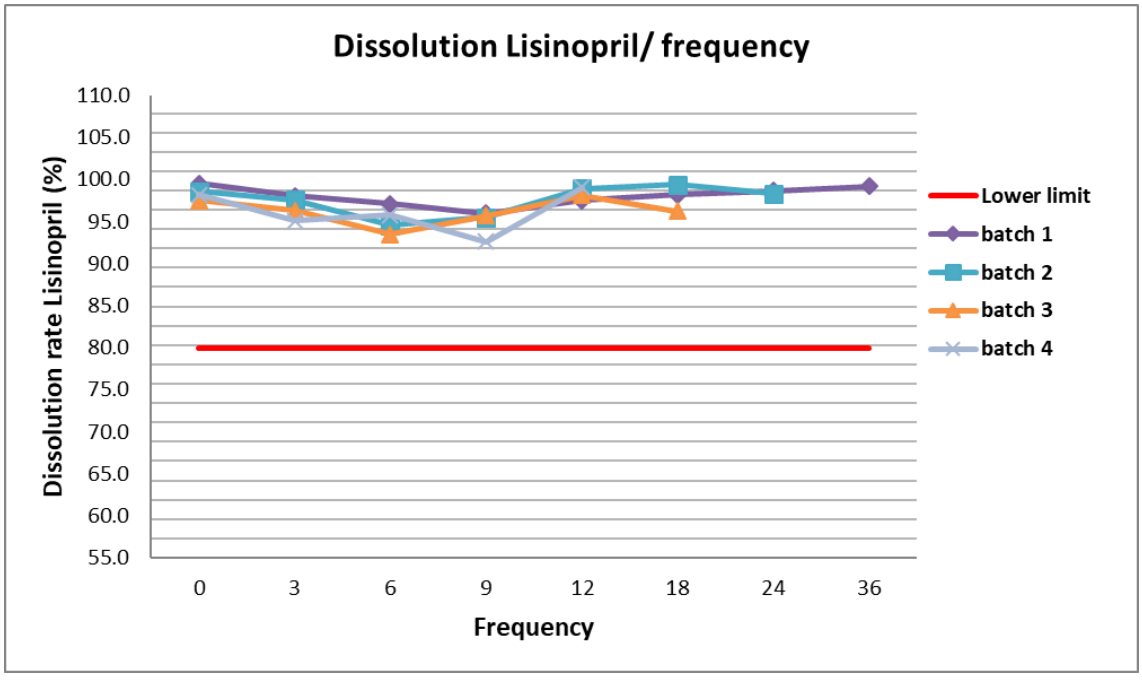

Fig. 5. Trending analysis of Lisinopril assay.

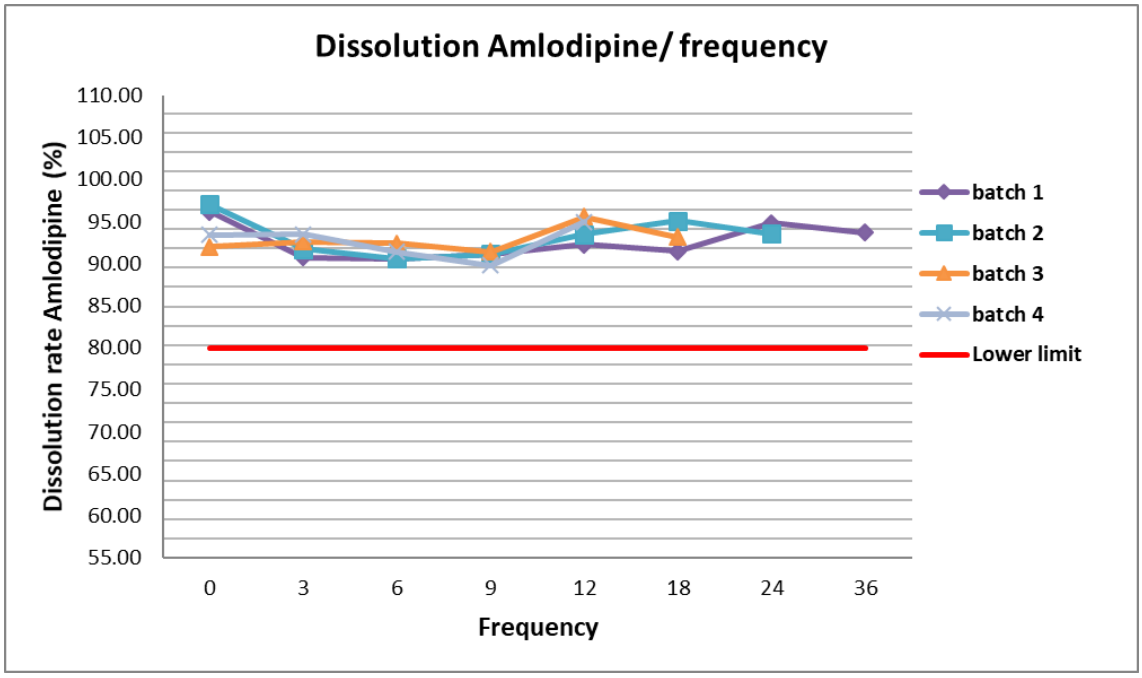

Fig. 6. Trending analysis of Amlodipine assay.

Table 3. Trending analysis of the parameter related and degradation compound from lisinopril: impurity C, any unspecified impurity and total impurities in Lisinopril/Amlodipine tablets 20mg/10mg

Frequency (months) / batch	0	*3*	*6*	*9*	*12*	*18*	*24*	*36*
				Impurity C				
batch 1	0.00	0.00	0.00	0.06	0.06	0.07	0.08	0.09
batch 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
batch 3	0.00	0.00	0.00	0.00	0.00	0.00		
batch 4	0.00	0.00	0.00	0.00	0.00			
				Any unspecified impurity				
batch 1	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10
batch 2	0.10	0.10	0.10	0.10	0.10	0.10	0.10	
batch 3	0.12	0.06	0.06	0.06	0.06	0.06		
batch 4	0.06	0.06	0.06	0.06	0.06			
				Total impurities				
batch 1	0.19	0.18	0.10	0.23	0.24	0.24	0.37	0.18
batch 2	0.15	0.21	0.10	0.10	0.10	0.10	0.15	
batch 3	0.26	0.21	0.06	0.06	0.06	0.06		
batch 4	0.06	0.13	0.06	0.06	0.06			

An estimate of the expected result at any given time point for a given batch is specified by the following relation:

- for the Impurity D content: Response = 0.00 + 0.000 * Frequency
- for the Impurity F content: Response = 0.03 - 0.001 * Frequency
- for the Any unspecified impurity content: Response = 0.00 + 0.000 * Frequency
- for the Total impurities content: Response = 0.03 - 0.001 * Frequency

Results for this investigated parameter remain within the specification requirements without potential OOS result during shelf life.

Microbiological purity

Regarding microbiological purity, the results show no

discernible change over time for Total Aerobic Microbial Count (TAMC), Total Combined Yeasts and Molds (TYMC), and Escherichia coli. All results meet the shelf-life requirements. Tabular presentation of parameter TAMC, TYMC and Escherichia coli are given in Table 5.

Overall results

From the results presented above it can be observed that the parameters assay, dissolution rate, related and degradation products and microbiological purity considered as CQAs, reveal similar profile for all batches tested at the same conditions. Parameters assay, dissolution rate and related and degradation products are considered as stability indicating parameters and consequently are tested on every testing frequency stated in the stability plan and protocol. Parameter microbiological purity is not considered as stability indicating parameter and consequently is tested only at the beginning and at the end of the stability test period as stated in the stability plan and protocol. The results of all batches follow a trend suggesting that there is no statistically significant difference in parameters trends. Results for all investigated parameters from shelf-life specification remain within the specification requirements without potential OOS result during shelf life.

The stability study results indicate that Lisinopril/Amlodipine tablets 20mg/10mg remains within the defined shelf-life specifications for all evaluated parameters, despite minor variability. This data reinforces the ongoing quality, safety, and efficacy of the product throughout its shelf life.

Importance of trend analysis for consistent performance

Trend analysis in stability studies is a vital tool for predicting potential out-of-specification (OOS) results within the estimated shelf life of fixed combination medicinal products.

Also, common sense would indicate that trend analysis could predict the likelihood of future OOS results, proactive identification of potential OOS. Avoiding potential issues with marketed product, as well as potential regulatory issues, is a sufficient basis to apply trending analysis as a best practice in the industry.

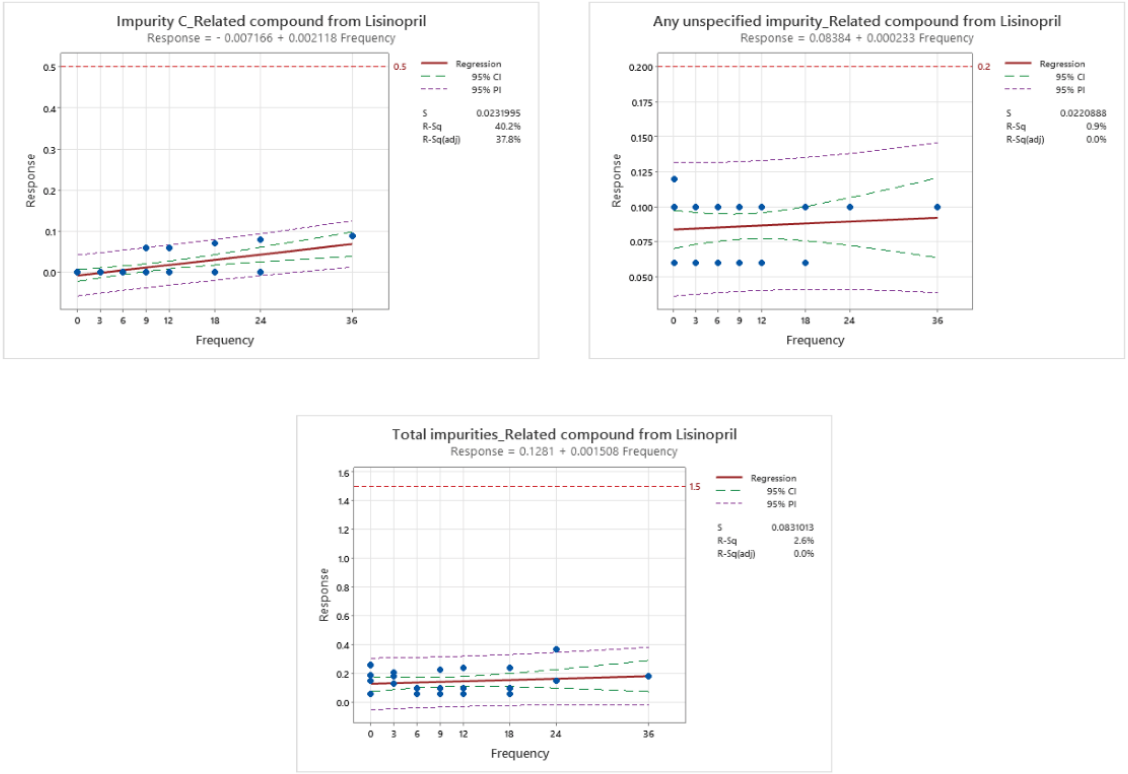

Fig. 7. Graphical presentation of regression analysis (Response versus Frequency) for the parameter related and degradation compound from Lisinopril: impurity C, any unspecified impurity and total impurities in Lisinopril/Amlodipine tablets 20mg/10mg.

Table 4. Trending analysis of the parameter related and degradation compounds from Amlodipine: Impurity D, Impurity F, Any unspecified impurity and Total impurities in Lisinopril/Amlodipine tablets 20mg/10mg

Frequency (months) / batch	0	*3*	*6*	*9*	*12*	*18*	*24*	*36*
				Impurity D / frequency				
batch 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
batch 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
batch 3	0.00	0.00	0.00	0.00	0.00	0.00		
batch 4	0.00	0.00	0.00	0.00	0.00			
				Impurity F / frequency				
batch 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
batch 2	0.09	0.09	0.09	0.09	0.10	0.09	0.00	
batch 3	0.00	0.00	0.00	0.00	0.00	0.00		
batch 4	0.00	0.00	0.00	0.00	0.00			
				Any unspecified impurity / frequency				
batch 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
batch 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
batch 3	0.00	0.00	0.00	0.00	0.00	0.00		
batch 4	0.00	0.00	0.00	0.00	0.00			
				Total impurities / frequency				
batch 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
batch 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
batch 3	0.00	0.00	0.00	0.00	0.00	0.00		
batch 4	0.00	0.00	0.00	0.00	0.00			

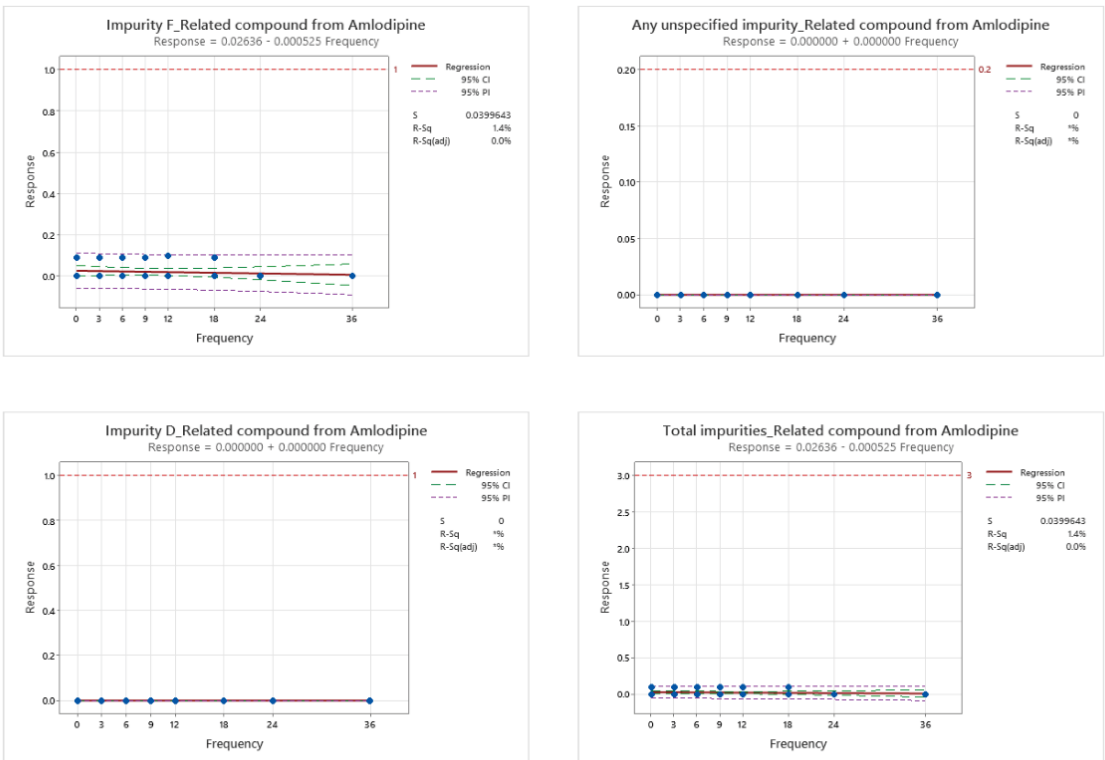

Fig. 8. Graphical presentation of regression analysis (Response versus Frequency) for the parameter related and degradation compound from Amlodipine: impurity D, impurity F, any unspecified impurity and total impurities in Lisinopril/Amlodipine tablets 20mg/10mg.

Table 5. Trending analysis of the parameter Total aerobic microbial count (TAMC), Total combined yeast/molds (TYMC) and presence of Escherichia coli in Lisinopril/Amlodipine tablets 20mg/10mg

Frequency (months) / batch	0	*3*	*6*	*9*	*12*	*18*	*24*	*36*
Total aerobic microbial count (TAMC) (CFU/g) / frequency								
batch 1	< 100cfu/g	/	/	/	/	/	< 100cfu/g	< 100cfu/g
batch 2	< 100cfu/g	/	/	/	/	/	< 100cfu/g	
batch 3	< 100cfu/g	/	/	/	/	/		
batch 4	< 100cfu/g	/	/	/	/			
Total combined yeast/molds (TYMC) (CFU/g) / frequency								
batch 1	< 10cfu/g	/	/	/	/	/	< 10cfu/g	< 10cfu/g
batch 2	< 10cfu/g	/	/	/	/	/	< 10cfu/g	
batch 3	< 10cfu/g	/	/	/	/	/		
batch 4	< 100cfu/g	/	/	/	/			
Escherichia coli /g / frequency								
batch 1	Conforms	/	/	/	/	/	Conforms	Conforms
batch 2	Conforms	/	/	/	/	/	Conforms	
batch 3	Conforms	/	/	/	/	/		
batch 4	Conforms	/	/	/	/			

Conclusion

By systematically evaluating stability data over time, trend analysis enables early detection of deviations, supports data-driven decision-making, and enhances overall quality control. The insights gained from identifying trends not only refine shelf-life predictions but also facilitate proactive risk management and regulatory compliance. Ultimately, leveraging trend analysis contributes to ensuring the consistent quality, safety, and efficacy of pharmaceutical products throughout their intended shelf life. Furthermore, trend analysis supports more reliable shelf-life predictions, optimizing inventory management and reducing waste.

Monitoring and interpreting stability data trend are integral to maintaining pharmaceutical product quality, safety, and compliance. By effectively tracking data, identifying patterns, and making informed decisions, pharmaceutical professionals can ensure that patients receive safe and effective medications throughout a product's lifecycle.

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Резиме

Предности на тренд анализата во студиите на стабилност за предвидување на потенцијален резултат надвор од спецификациските граници за време на рокот на траење на лек

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Клучни зборови: студии за стабилност, евалуација на податоци за стабилност, долгорочна стабилност, лизиноприл, амлодипин, таблети

Студиите за стабилност се неопходни за регистрација на фармацевтски производи обезбедувајќи витални податоци за оценување на конзистентноста помеѓу сериите, следење на критичните атрибути и осигурување на квалитетот, безбедноста и ефикасноста на производот во текот на рокот на траење.

Идентификацијата на потенцијалните проблеми, како што се можни резултати надвор од спецификациите (OOS) и обезбедувањето на квалитетот на податоците често се олеснува со користење на објективни методи за анализа на трендови на податоците за стабилност.

Целта на истражувањето беше да се истражат предностите на анализата на трендовите во студиите за стабилност, истакнувајќи го нејзиното значење во предвидување на резултатите од OOS и обезбедувајќи конзистентни перформанси на фармацевтските производи во рамките на нивниот проценет рок на траење.

За да се проценат податоците за стабилноста и да се најде моделот на податоци што укажува на промена со текот на времето, студиите за стабилност за таблетите Лизиноприл/Амлодипин 20 mg/10 mg беа подложени на трендовска анализа врз основа на податоците од годишните или рутинските студии за стабилност. Анализата на трендовите беше изведена за да се оцени дали податоците покажуваат тренд на зголемување или намалување (промена на средната вредност) за стабилноста што ги покажува параметрите со текот на времето или податоците не укажуваат на забележлива промена, како и предвидување на потенцијалните резултати на OOS за време на рокот на траење. Регресивната анализа како статистичка алатка за анализа на трендовите се смета за соодветен пристап за евалуација на податоците за стабилноста за квантитативен атрибут.