A REVIEW OF HEALTH-RELATED QUALITY OF LIFE (HRQL) CLAIMS IN LABELS OF ASTHMA PRODUCTS – CAN WE CONSIDER THE ASTHMA QUALITY OF LIFE QUESTIONNAIRE (AQLQ) AS A POTENTIALLY ACCEPTABLE MEASURE FOR QUALIFICATION?

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Background and Objectives

- The asthma quality of life questionnaire (AQLQ) is a condition-specific measure which evaluates four domains of health-related quality of life (HRQL) important in asthmatic adults: activity limitation, symptoms, emotional function, and environmental exposure.

- The objectives of this study were to identify:
  1) How many HRQL claims were obtained in the label of asthma products using the AQLQ;
  2) HRQL measures used in trials but not mentioned in label;
  3) The reasons why to discard these measures.

Methods

- The PROLabels database (www.mapi-prolabels.org/) was searched on 12/27/2014 using "asthma" as a key word for therapeutic indication. Medical Reviews (FDA) and Assessment Reports (EMA) were retrieved on the corresponding websites and analyzed.

Results

- Out of thirty-seven products approved for asthma (five by the EMA, and 32 by the FDA), twenty-five had a PRO claim in their label.

- Five of them had a HRQL claim (see Table 1):
  - Symbicort (budesonide/formoterol fumarate dehydrate - FDA)
  - Advair HFA (fluticasone propionate/salmeterol xinafoate - FDA)
  - Advair Diskus (fluticasone propionate/salmeterol xinafoate - FDA)
  - Dulera (mometasone furoate/formoterol fumarate – FDA)
  - Xolair (omalizumab - EMA)

  In all cases, the HRQL evaluation was performed using the AQLQ.

- Of the 20 products with a PRO claim (mainly symptoms), but not a HRQL claim, seven had no HRQL evaluation performed, three had no medical review available, and ten had a HRQL evaluation using either the AQLQ, Mini AQLQ or PAQLQ (n=8), and/or the SF-36 (n=3) [one product was evaluated with the AQLQ and the SF-36]. See Table 2.

  The main reasons provided for not including HRQL data in the label were:
  - lack of statistical significance between treatment groups,
  - or data not reaching clinical significance.

  In one case (omalizumab), the FDA argued about the improper use of the AQLQ. See Table 2.

- Of the 12 products with no PRO claim in label (three EMA, nine FDA), four had no medical review available, six had no HRQL evaluation, and two had a HRQL evaluation using the AQLQ: one had no results available in the regulatory documents, and for the second, no statistical differences were shown between the groups.

Table 1. Products with an HRQL label (search dated 12/27/2014 – PROLabels)

AGENCY	INN	BRAND NAME	DATE OF APPROVAL	HRQL label
FDA	fluticasone propionate - salmeterol xinafoate	**Advair Diskus**	24/08/2000	**Study 1: Clinical Trial With ADVAIR DISKUS 100/50** The subjective impact of asthma on patients' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared to placebo). **Study 2: Clinical Trial With ADVAIR DISKUS 250/50** Patients receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared to placebo).
FDA	fluticasone propionate - salmeterol xinafoate	**Advair HFA**	08/06/2006	**Trial 1: Clinical Trial with ADVAIR HFA 45/21 Inhalation Aerosol** The subjective impact of asthma on subjects' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Subjects receiving ADVAIR HFA 45/21 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.14 [95% CI: 0.85, 1.44] compared with placebo).
FDA	mometasone furoate - formoterol fumarate	**Dulera**	22/06/2010	**Trial 1: Clinical Trial with DULERA 100 mcg/5 mcg** The subjective impact of asthma on patients' health-related quality of life was evaluated by the Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). A change from baseline >0.5 points is considered a clinically meaningful improvement. The mean difference in AQLQ between patients receiving DULERA 100 mcg/5 mcg and placebo was 0.5 [95% CI 0.32, 0.68].
FDA	budesonide - formoterol fumarate dihydrate	**Symbicort**	21/07/2006	**Study 1: Clinical Study with SYMBICORT 160/4.5:** The subjective impact of asthma on patients' health related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of >0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93] compared to placebo). **Study 2: Clinical Study with SYMBICORT 80/4.5** Efficacy results for other secondary endpoints, including quality of life, were similar to those observed in Study 1.
EMA	omalizumab	**Xolair**	25/10/2005	Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Table 2. List of products with a PRO claim (not HRQL)

Agency	INN	Brand Name	Date of Approval	HRQL Evaluation (if any)	Reasons for not including HRQL evaluation in label (data from medical review or assessment reports)
FDA	zafirlukast	Accolate	26/09/1996	**No HRQL evaluation**	
FDA	ciclesonide	Alvesco	10/01/2008	**No HRQL evaluation**	
FDA	mometasone furoate	Asmanex HFA	25/04/2014	AQLQ	**Study P04334**: For the AQLQ, the score at endpoint for MF 200 group was statistically significantly greater than that of the placebo group, but the change did not reach the established Minimal Clinically Important Difference (MCID) of >0.5 (0.38, p<0.05). **Study P04431**: The changes reached clinical significance for only the MF/F 200/10 group (0.58).
FDA	mometasone furoate	Asmanex Twisthaler	30/03/2005	SF-36 A validated asthma specific HRQL module	**Studies C96-136 and C96-137**: Results were not statistically significant. In addition, it was stated that SF-36 is not validated in asthmatic patients.
FDA	triamcinolone acetonide	Azmacort	23/04/1982	**Medical review of approval not available**	
FDA	fluticasone propionate	Flovent Diskus	29/09/2000	AQLQ SF-36	AQLQ: Evaluated in four studies (2002, 2006, 2004, 2005). Only 2005 study provided striking results not replicated. SF-36: Included only in study (2002) - statistical differences in only six out of nine domains.
FDA	fluticasone propionate	FloventHFA	14/05/2004	AQLQ	**Study 3007**: Results were clinically meaningful + statistical significance demonstrated for QOL. **Study 3008**: Only FP 440 group had clinically meaningful results.
FDA	formoterol fumarate	Foradil Aerolizer	16/02/2001	**No HRQL evaluation**	
FDA	formoterol fumarate	Foradil Certihaler	15/12/2006	Mini AQLQ	**Study 2302**: Small changes (did not reach clinical meaningfulness), not statistical differences between formoterol and placebo. **Study 2303**: Changes did not reach clinical meaningfulness.
FDA	budesonide	Pulmicort Flexhaler	12/07/2006	**No HRQL evaluation**	
FDA	budesonide	Pulmicort Respules	08/08/2000	**No HRQL evaluation**	
FDA	budesonide	Pulmicort Turbuhaler	24/06/1997	**Medical review of approval not available**	
FDA	beclomethasone dipropionate	Qvar	15/09/2000	AQLQ	**Study 1129**: The difference in assessment between each of the BDP groups and the placebo group was statistically significant, but of unclear clinical significance. **Study 1163**: There was no clinically significant difference between the change in QOL seen after administration of BDP-HFA and BDP-CFC.
EMA	fluticasone furoate - vilanterol trifenatate	Revinty Ellipta	02/05/2014	**No HRQL evaluation**	
FDA	salmeterol xinafoate	Serevent	04/02/1994	**Medical review of approval not available**	
FDA	salmeterol xinafoate	Serevent Diskus	19/09/1997	. Study 1: Acute Short Form-36 (SF-36), Greg Sleep Measure Scale and Living With Asthma (LWA-20A) questionnaire . Study 2: Parent/guardian was also asked to complete the Health-Related Quality of Life and Device Satisfaction Questionnaires.	No results provided in section 9 (Overall review of efficacy).
FDA	montelukast sodium	Singulair (Granule)	26/07/2002	**No HRQL evaluation**	
FDA	montelukast sodium	Singulair (Tablet)	20/02/1998	AQLQ	**Study 031**: No statistical significant difference from placebo in all domains, No MID pre-specified and no categorical analysis based on an MID was performed. The difference >.5 in MID was never achieved. **Study 020**: Idem as above. Beclomethasone was statistically superior to montelukast in these analyses and achieved a MID for the activity, symptoms emotions and total domains. **Study 015**: Statistically significant differences were not demonstrated for QOL. **Study 029**: Montelukast plus beclomethasone was not superior to beclomethasone alone for any domain. Beclomethasone was superior to montelukast and placebo for the domains of symptoms and emotions why beclomethasone was only superior to montelukast for the domain of activity and environment. MID criteria (0.5 unit MID) were not met for any of the between group comparisons for the overall or any individual QOL domain (except for symptoms in which M+B was 0.51 greater than placebo) over the 16-week treatment period.
FDA	montelukast sodium	Singulair (Tablet, chewable)	20/02/1998	PAQLQ	**049**: No "win" was prespecified for this endpoint and the sponsor's analysis showing statistical significance in all domains and overall did not follow the minimally important difference interpretation specified by "blank" and colleagues in their publication.
FDA	omalizumab	Xolair	20/06/2003	AQLQ	Same data as for EMA. No claim because reviewer mentioned that AQLQ was not used properly.

Conclusion

- This review has shown that all HRQL claims in asthma product labels were obtained using the AQLQ, a validated measure in asthma patients with a recognized minimally important difference enabling a clear interpretation of results. For these reasons the AQLQ could be considered as a potentially acceptable measure for regulatory qualification.

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ISPOR 20th Annual International Meeting – May 16-20th, 2015 – Philadelphia, PA, USA